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Special session

Limiting the Attributable Mortality of Healthcare-Associated Infection & Multidrug Resistance

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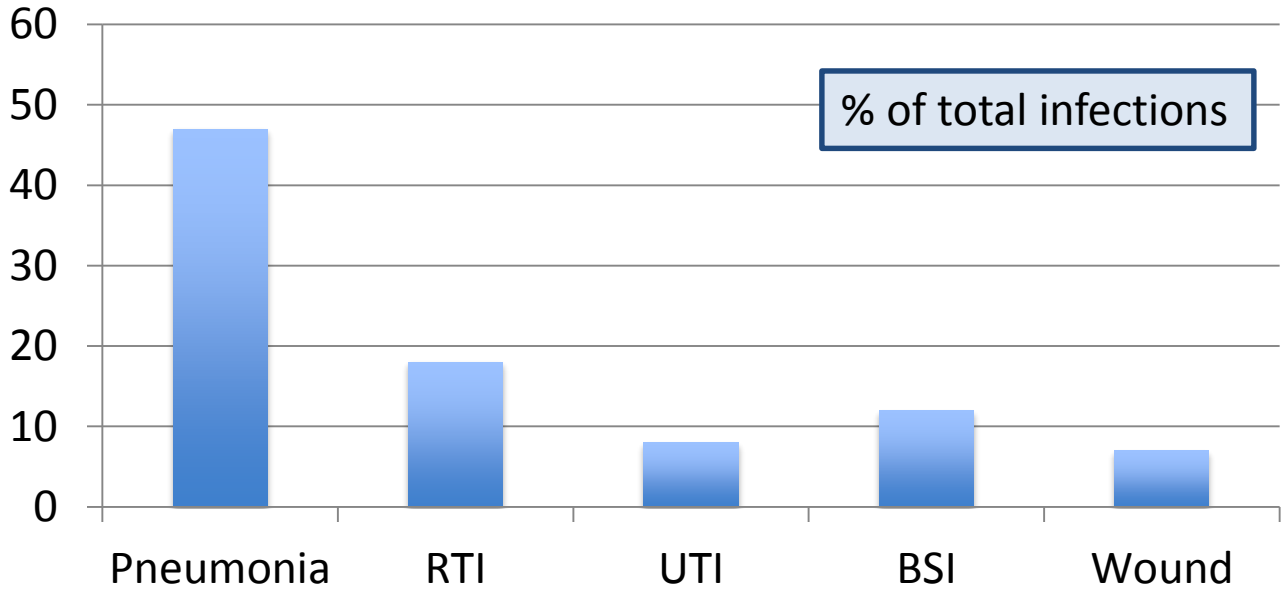
Disclosures

- Nothing to disclose

Introduction

Healthcare associated infection (HAI)

- Point-prevalence study (n=10,038 ICU patients)
  - Infected: n=4,501 (44.8%)
  - ICU-acquired: n=2,046 (20.6%)



Vincent et al. JAMA 1995

Introduction

Healthcare associated infection (HAI)

- Risk profile:
  - ➔ severity of acute illness
  - ➔ underlying conditions
  - ➔ aging population
  - ➔ immunosuppressive agents
  - ➔ invasive devices
- Medical progress ➔ growing pool of high-risk patients

Introduction

Healthcare associated infection (HAI)

- 1980s – 1990s perception of HAI in ICUs:
  - ➔ generally unavoidable
  - ➔ high mortality

Introduction

Relationship HAI and Mortality

- ICUs → highest rates of HAI
  → highest disease severity

- ICU patients → high risk for HAI and death

➔ discriminate **attributable** from **associated** mortality

Introduction

Relationship HA-BSI and Mortality

- Bacteremia in ICU patients
  - → associated mortality: 50%
  - → attributable mortality: 35%

- Candidemia ICU/general ward patients
  - → associated mortality: 57%
  - → attributable mortality: 38%

Pittet D, et al. JAMA 1994
Wey SB, et al. Arch Intern Med 1988

Introduction

Relationship Candidemia and Mortality

- Outcome perception in ICU patients with candidemia in the 1990s

Survival

Death due to **candidemia** (attributable)

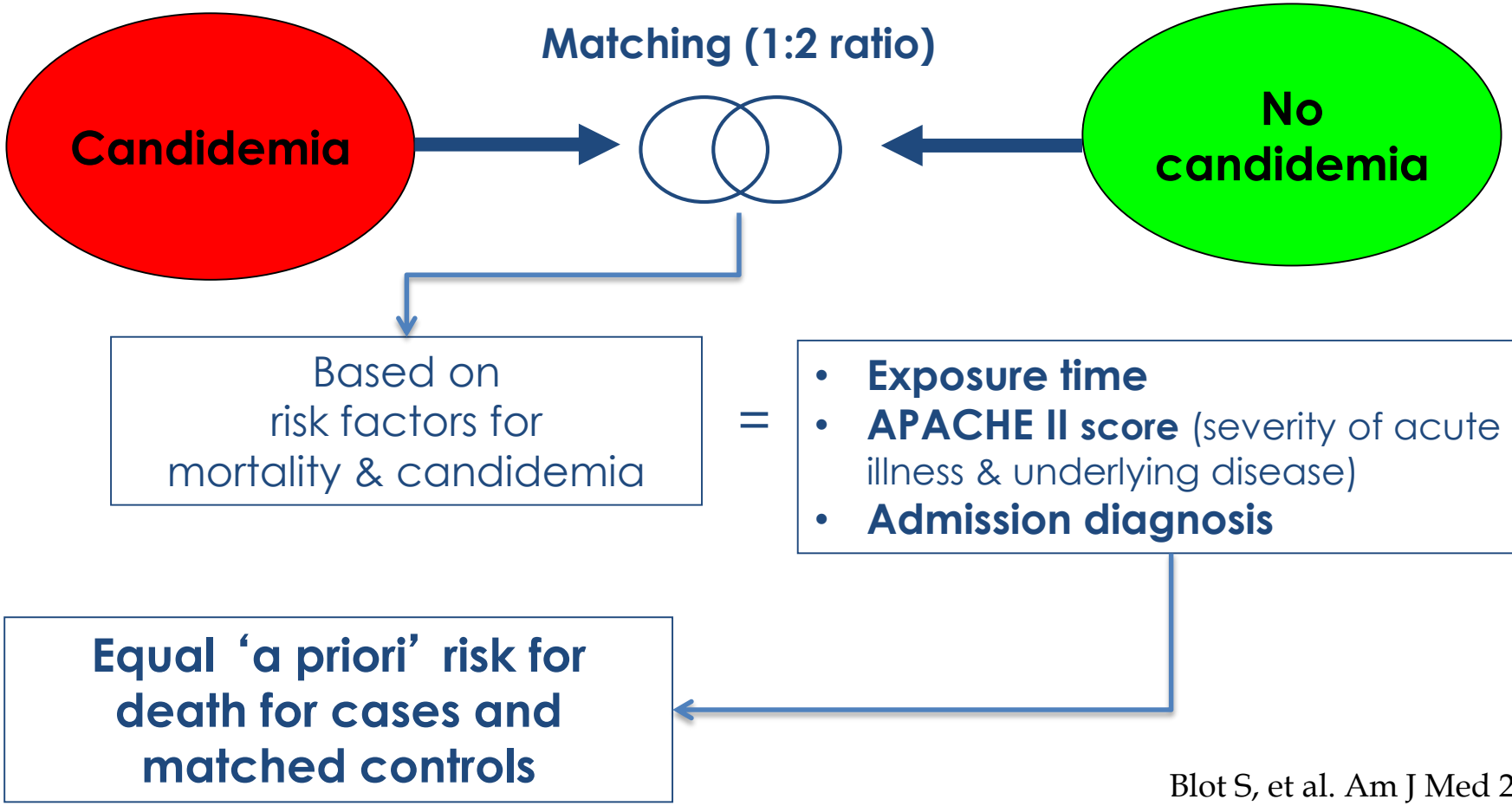
Death due to general **disease severity**

Wenzel R, et al. Clin Infect Dis 1995

Introduction

Attributable mortality of candidemia

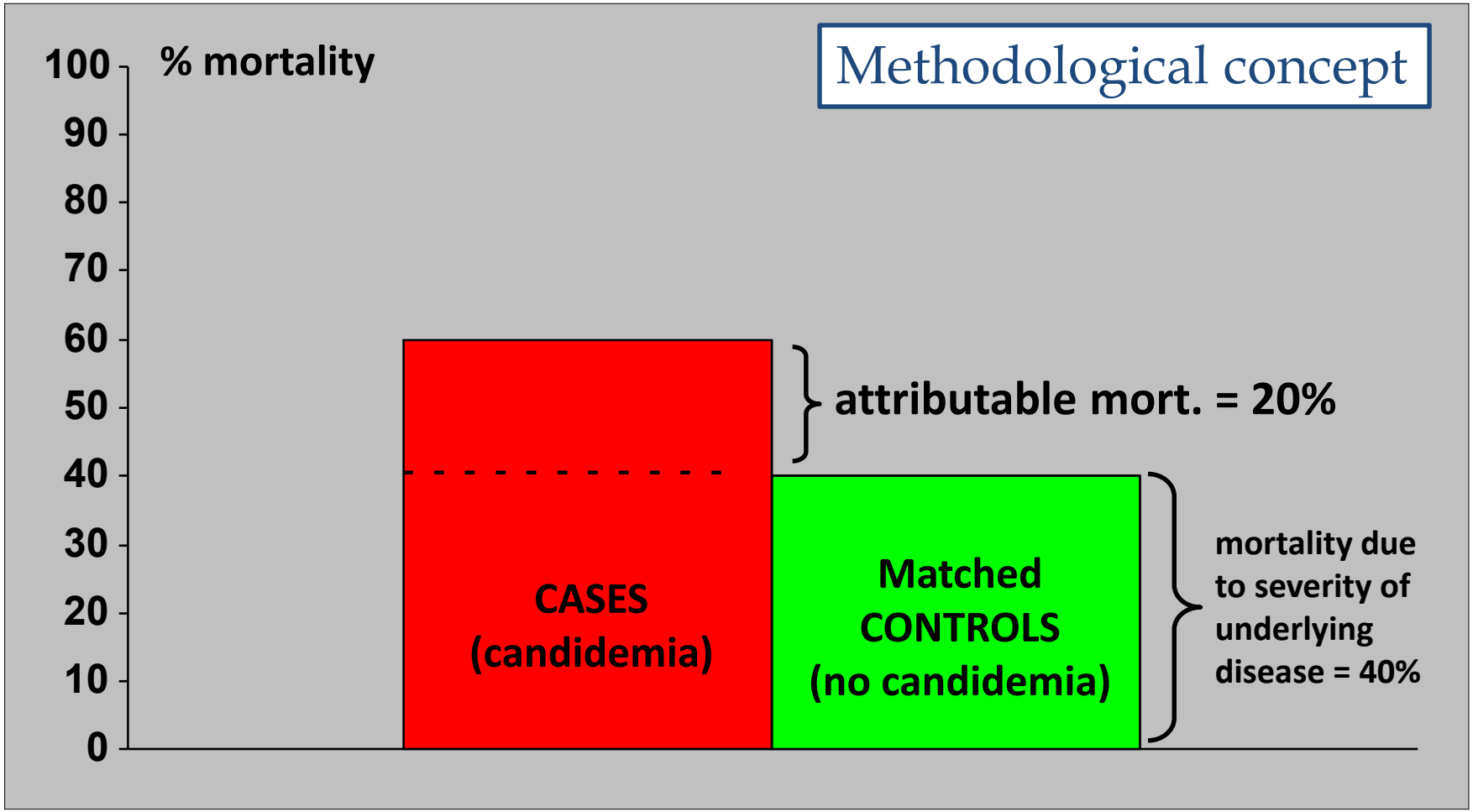
"Matched cohort" study design



Blot S, et al. Am J Med 2002

Introduction

Attributable mortality of candidemia



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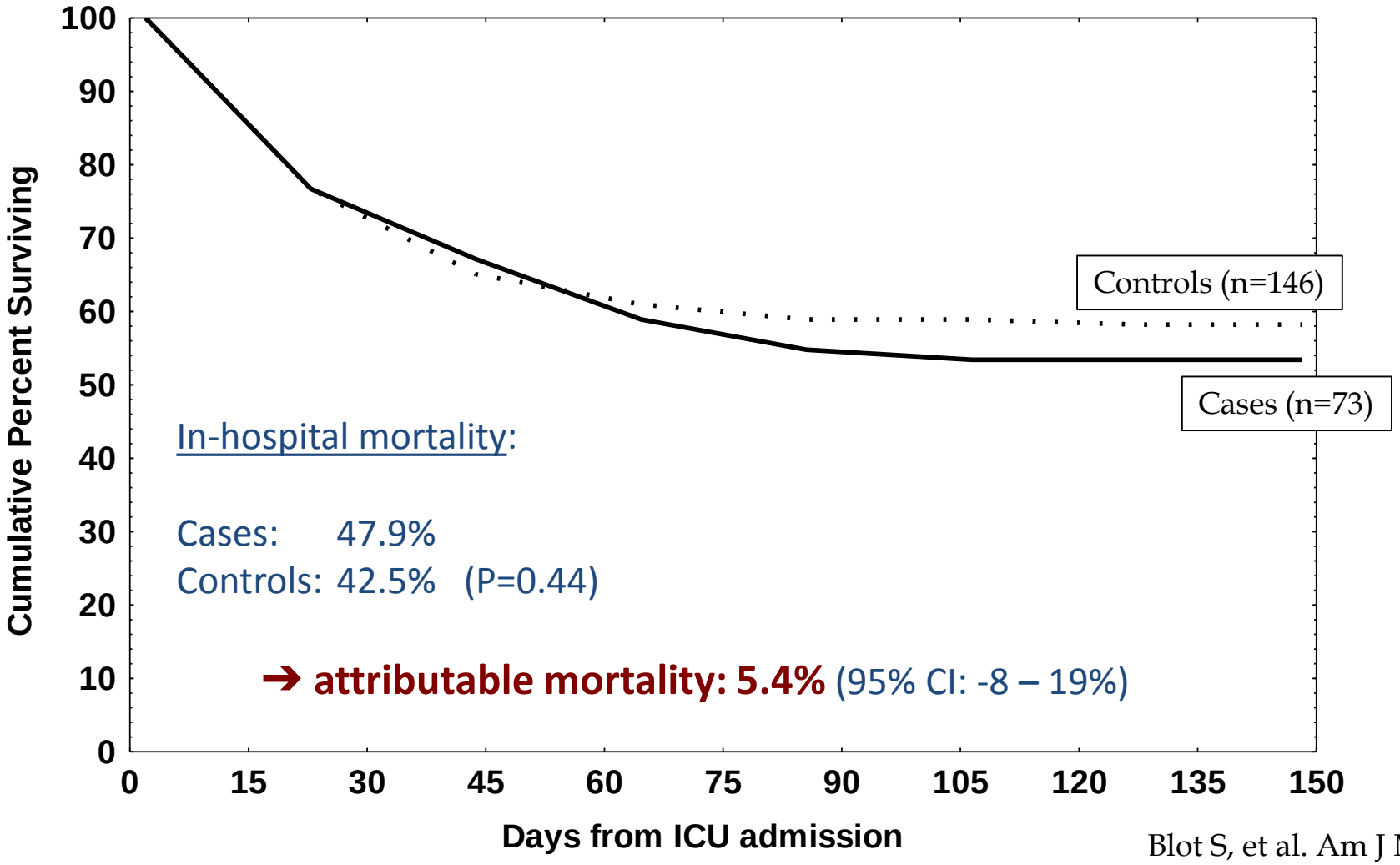
Attributable mortality of candidemia

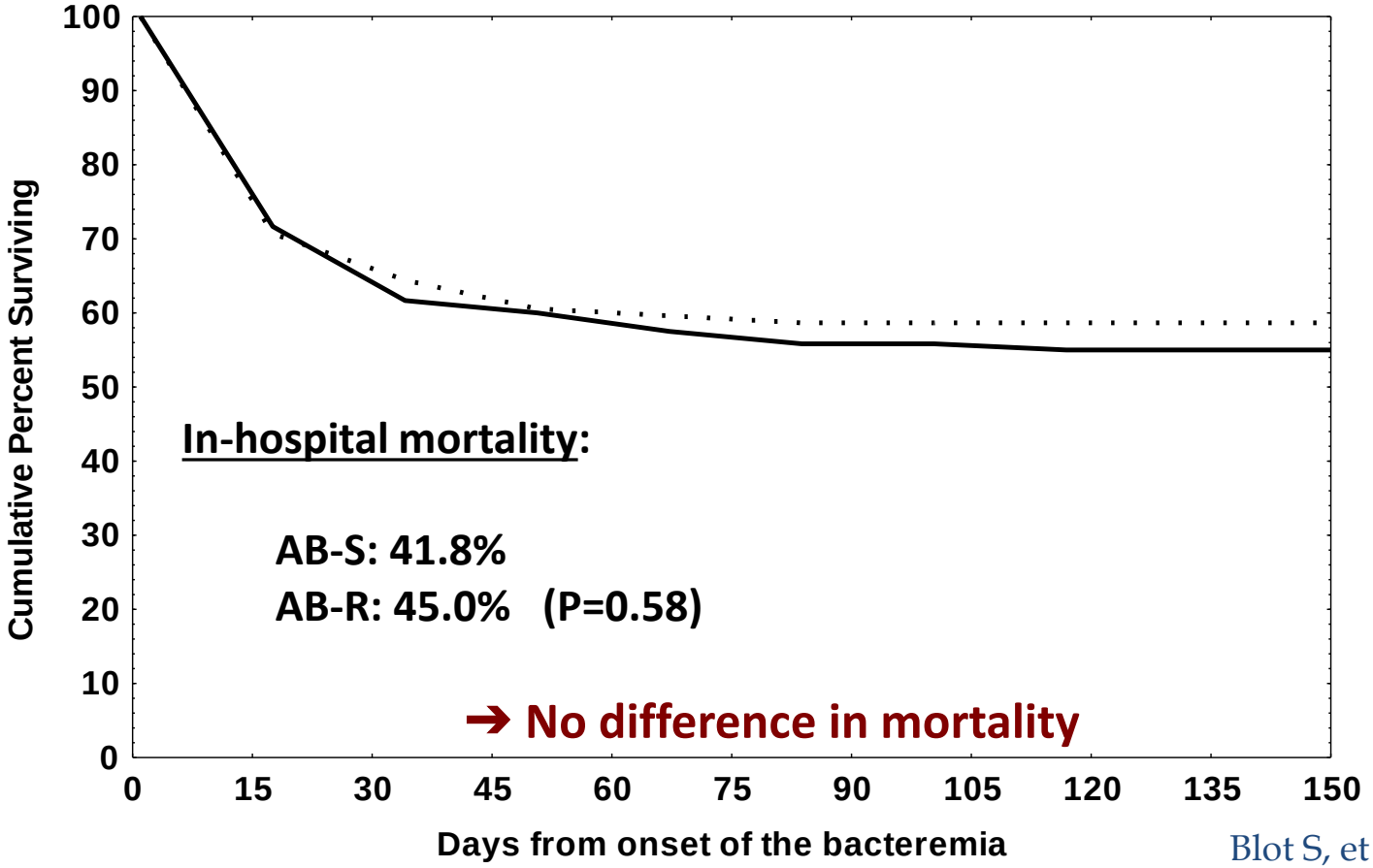


Blot S, et al. Am J Med 2002

Introduction

Relationship MDR & Mortality

Gram-negative bacteremia in ICU patients

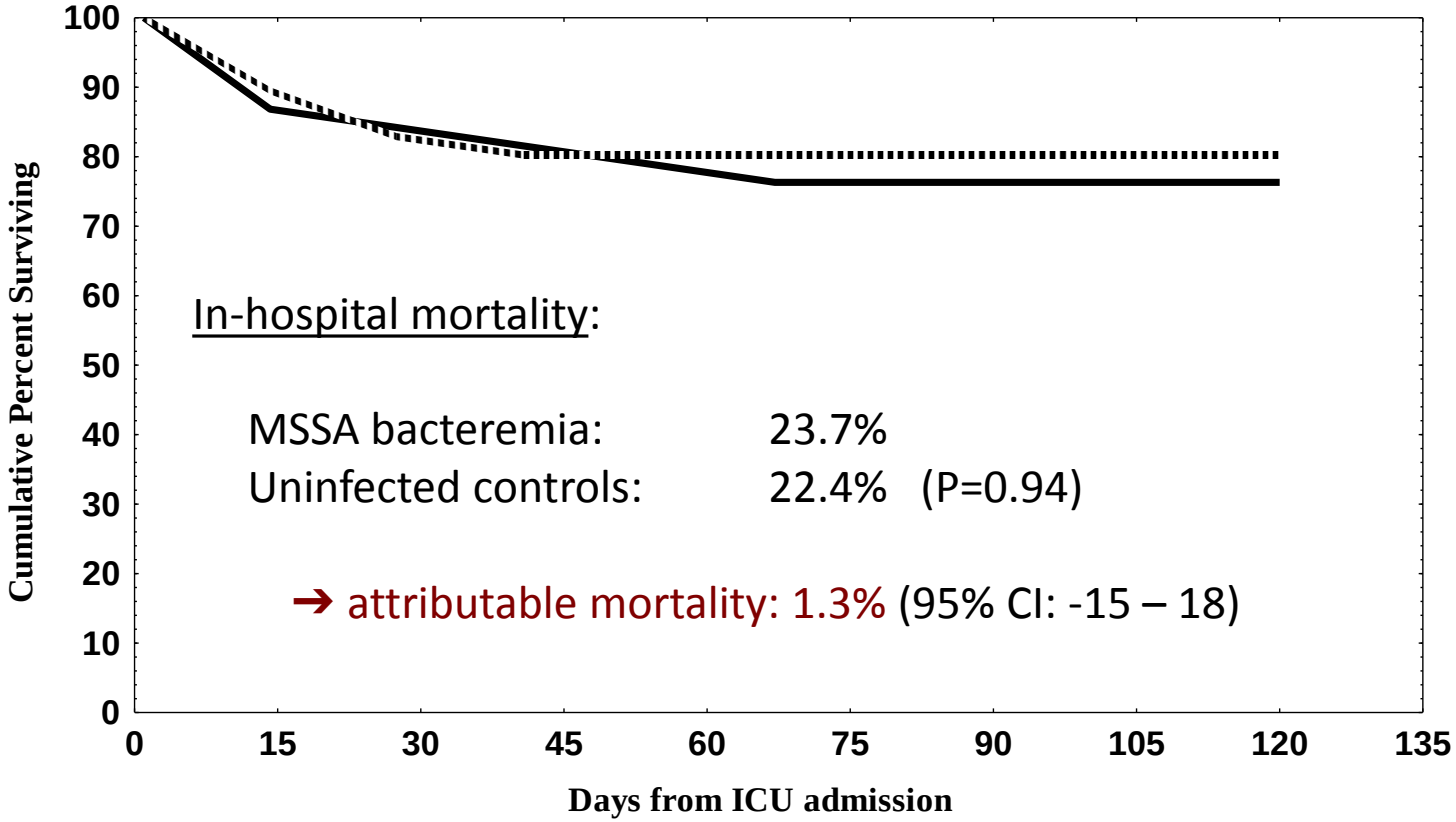


Blot S, et al. Clin Infect Dis 2002

Introduction

Relationship MDR & Mortality

MSSA bacteremia in ICU patients

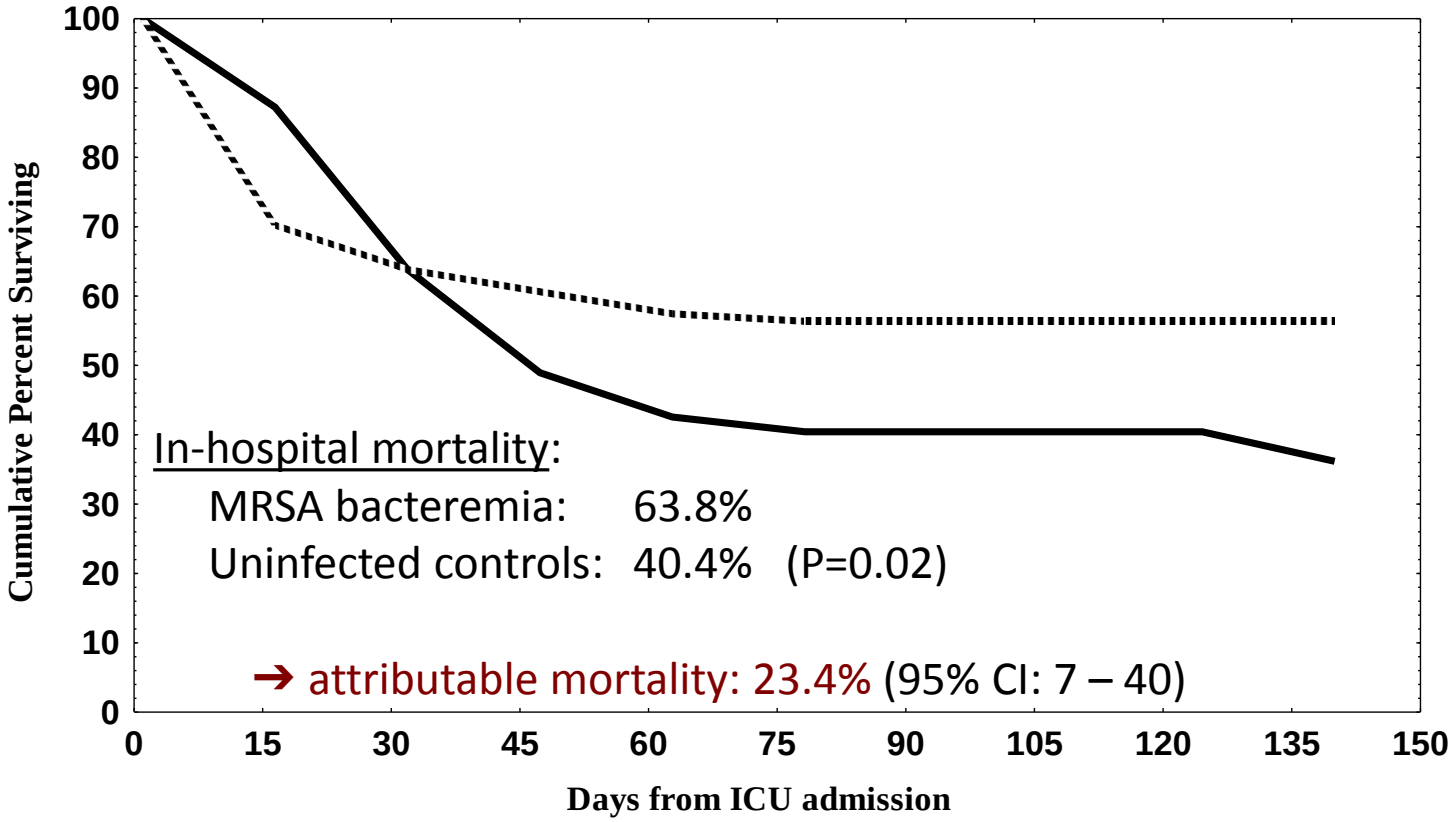


Blot S, et al. Arch Intern Med 2002

Introduction

Relationship MDR & Mortality

MRSA bacteremia in ICU patients



Blot S, et al. Arch Intern Med 2002

Introduction

Attributable mortality of Bloodstream infection

Author, journal, year	Focus	Mortality		Attributable mortality, % (95% CI)
		cases	controls	
Blot S, et al. Am J Med 2002	*Candida*	48%	43%	5% (-8–19)
Blot S, et al. Eur J Clin Microb Infect Dis 2002	*Klebsiella*	36%	37%	0%
Blot S, et al. Arch Intern Med 2002	*S. aureus*	24%	23%	1% (-15-18)
Blot S, et al. J Hosp Infect 2003	*P. aeruginosa*	62%	47%	15% (-1–31)
Blot S, et al. Intensive Care Med 2003	*A. baumannii*	42%	34%	8% (-10–25)
Blot S, et al. Chest 2003	*Enterobacter*	34%	38%	0%
Blot S, et al. Infect Control Hosp Epidem 2003	*E. coli*	44%	45%	0%
Hoste E, et al. J Am Soc Nephrol 2004	RRT pts.	70%	63%	7% (-9–21)
Blot S, et al. Clin Infect Dis 2005	Cath-related	28%	26%	2% (-6–10)
Brusselaers N, et al. Burns 2010	Burn pts.	12%	17%	0%

Introduction

Mortality of healthcare-associated infections

Author, journal, year	Focus	Mortality compared with unexposed patients
Vandewoude K, et al. J Hosp Infect 2004	Invasive aspergillosis	HR 1.9 (95% CI 1.2-3.0)
Agbath K, et al. Crit Care Med 2006	Bacteremic vs. non-bacteremic VAP	RR 2.9 (95% CI 1.1-7.5)
De Waele J, et al. Pancreas 2004	BSI after surgery for acute pancreatitis	57% vs. 35% (NS)
De Waele J, et al. Clin Infect Dis 2003	*Candida* infection in necrotizing pancreatitis	35% vs. 28% (p=0.41)
Benoit D, et al. Intensive Care Med 2005	Bacterial vs. non-bacterial compl. in hemato-pts.	OR 0.2 (95% CI 0.1-0.6)
Myny D, et al. Acta Clin Belg 2005	VAP	OR 0.8 (95% CI 0.4-1.5)
Blot S, et al. Crit Care Med 2009	BSI in old ICU pts. BSI in very old ICU pts.	HR 1.2 (95% CI 1.0-1.5) HR 1.8 (95% CI 1.4-2.4)
De Waele J, et al. Surg Infect 2008	BSI + intra-abd. infections	62% vs. 42% (p≤0.001)

Introduction

Low attributable mortality rates are not for free!

Matched cohort studies on Central Line-Associated Bloodstream Infection

Author	Source year	Number of cases	Number of controls	Attributable mortality
Soufir	ICHE 1999	n=38	n=76	26% (NS)*
Rello	AJRCCM 2000	n=49	n=49	0% (NS)
Renaud	AJRCCM 2001	n=26	n=26	12% (NS)
Rosenthal	Am J Infect Control 2003	n=142	n=142	25% (14 – 36%)
Blot	Clin Infect Dis 2005	n=176	n=315	2% (NS)
Garrouste-Orgeas	CID 2006	n=47	n=207	3% (NS)
Higuera	ICHE 2007	n=55	n=55	20% (p=0.06)

* NS after adjustment for covariates

Introduction

Determinants of Mortality in Severe HAI

Mortality~ genetic predisposition

~ age

~ underlying disease

~ site of infection

~ micro-organism + resistance pattern

~ anti-infective management

only "manageable" factor

Essentials in Anti-Infective Management

1. Early recognition of sepsis
2. First shot antimicrobial therapy: asap
3. Coverage of causative etiology
4. Adequate dosing
5. Infection prevention

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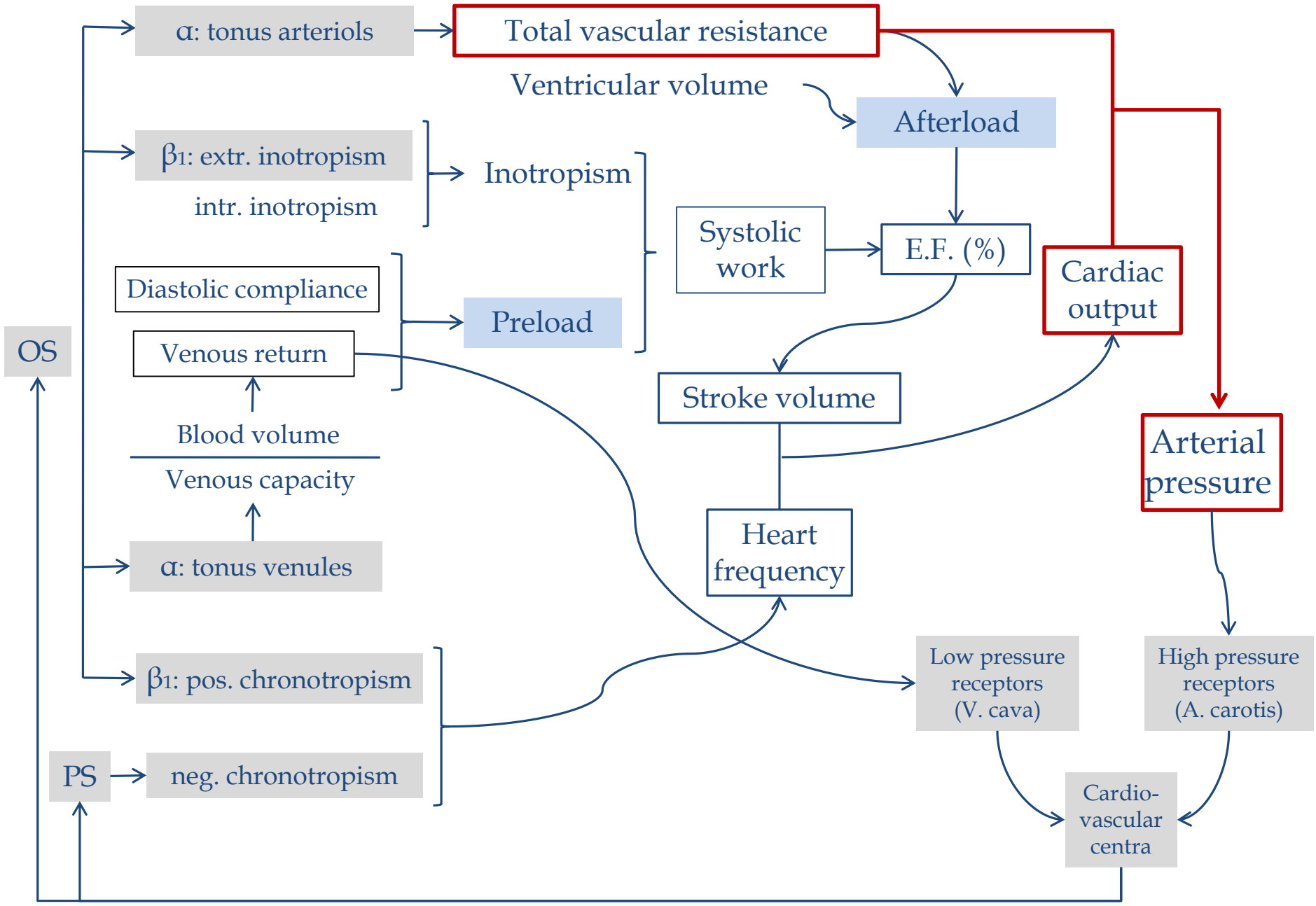
Early recognition of sepsis

- **Sepsis alert scores**
  - Checklist, regular bedside control
  - High NPV, Low PPV
  - Advantage: not diagnosing sepsis at a very late stage of the disease

Early recognition of sepsis

- **Task: detect discrete variations in vital signs**
  - Central vital sign = art. blood pressure
  - Decreasing ABP / hypotension = too late
  - Human body will do everything to keep ABP up
  - IC nurse must (also) focus on the mechanisms that precede overt ABP variation
  - E.g. heart rate



Observations prior to septic shock

Hypotension = late symptom of shock
Challenge = to sense compensation mechanisms and to prevent shock (and damage to vital organs) .

Observation	Possible meaning
↓ urine output	Peripheral vasoconstriction, Saving circulating blood volume for vital organs
Pallor, mottling, cold skin, cold extremities,…	
Tachycardia	Reflex triggered by ↓ venous return
↓ filling pressures (CVP, PCWP)	↓ blood volume (absolute hypovolemia) ↑ venous capacity (relative hypovolemia)
↑ cardiac output (C.O.)	may be early signal for evolving sepsis
Restlessness, confusion	Pending shock
Tachypnea	Compensation pending metabolic acidosis

Essentials in Anti-Infective Management

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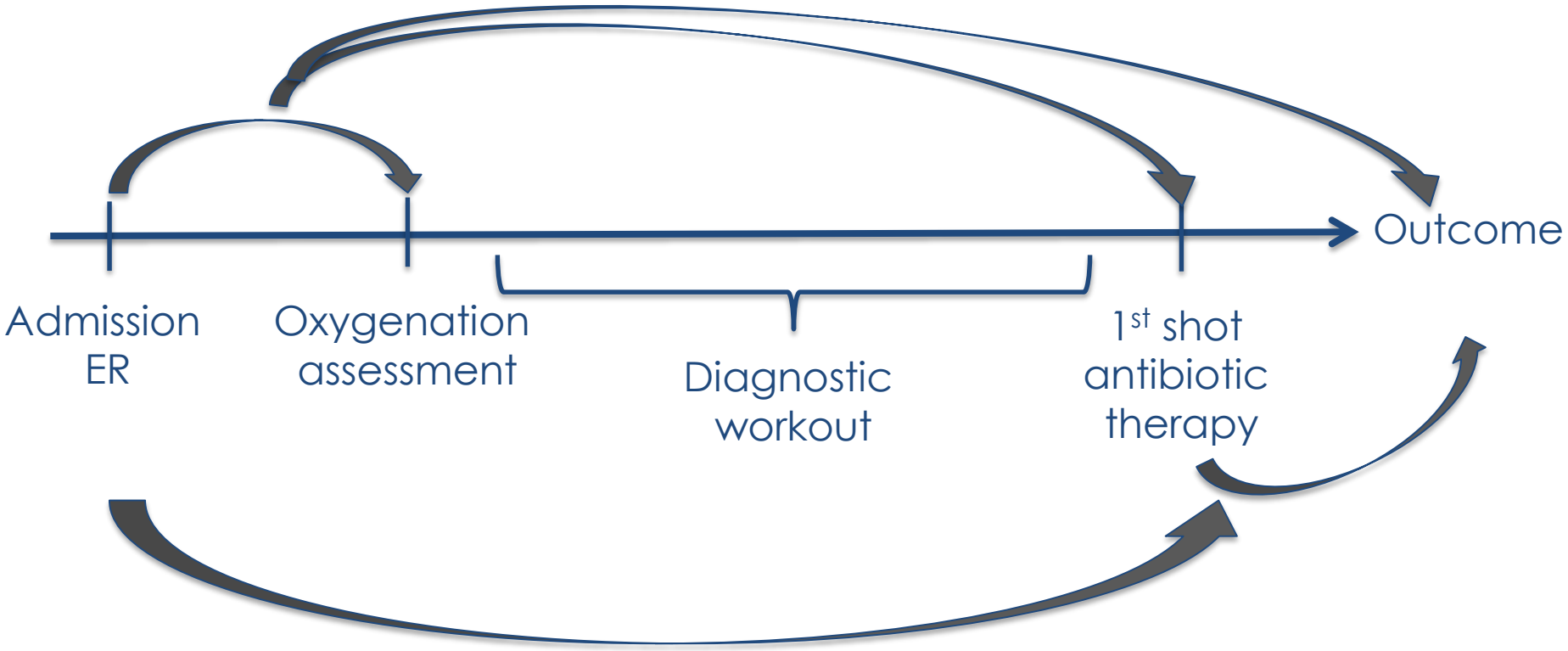
Basic conditions for optimal antibiotic therapy

First antibiotic dose without delay

- Start empiric antibiotic therapy asap (take relevant cultures first!)
- Surviving Sepsis Guidelines: <1 hr in septic shock / severe sepsis
- Strongly related to processes of care targetting mechanisms to detect sepsis at an early stage!

Dellinger RP, et al. Crit Care Med 2013

How to decrease time to 1st shot of antibiotic therapy in severe community-acquired pneumonia?



Blot S, et al. Crit Care Med 2007

Effects of delayed oxygenation assessment on time to antibiotic delivery and mortality in patients with severe community-acquired pneumonia*

Relationship Between Time to Oxygenation Assessment and Antibiotic Delivery

Delay in Oxygenation Assessment	Time (hrs) to First Antibiotic Dose[a]	*p*
>1 hr (n = 84)	6 (3–9)	<.001
≤1 hr (n = 269)	3 (2–5)	

Blot S, et al. Crit Care Med 2007

Effects of delayed oxygenation assessment on time to antibiotic delivery and mortality in patients with severe community-acquired pneumonia*

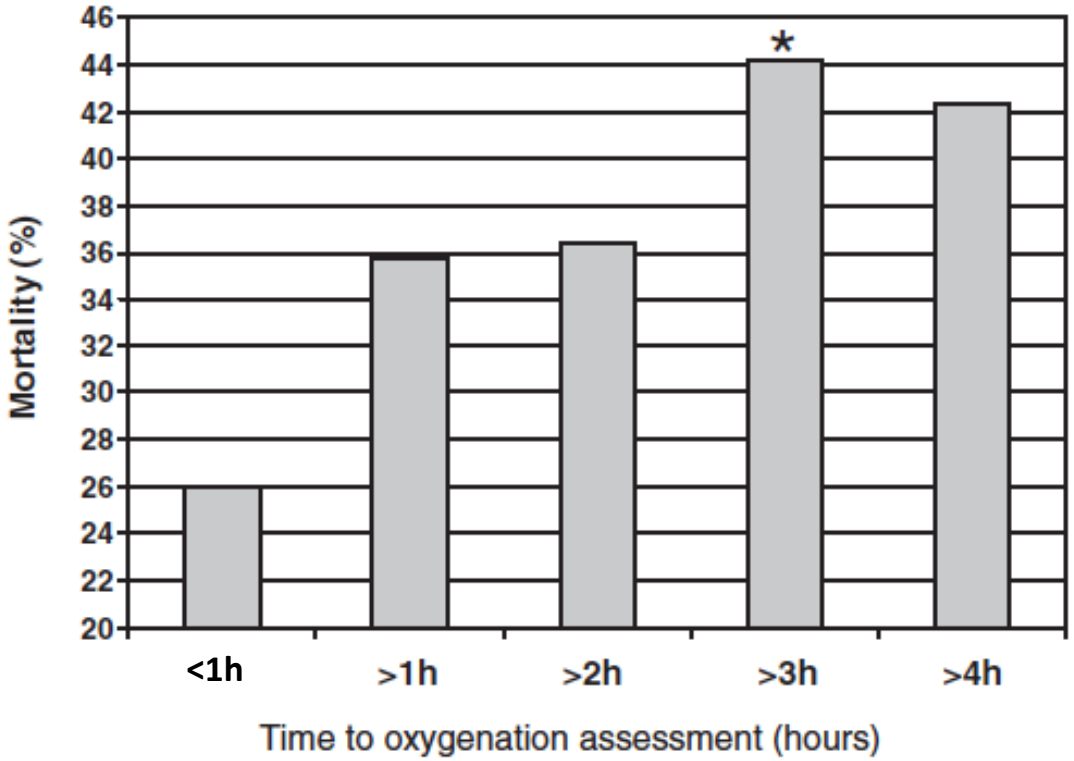


Figure 2. Mortality according to delay in oxygenation assessment. *Relative risk of death, 2.24 (95% confidence interval, 1.17 to 4.30).

Blot S, et al. Crit Care Med 2007

Essentials in Anti-Infective Management

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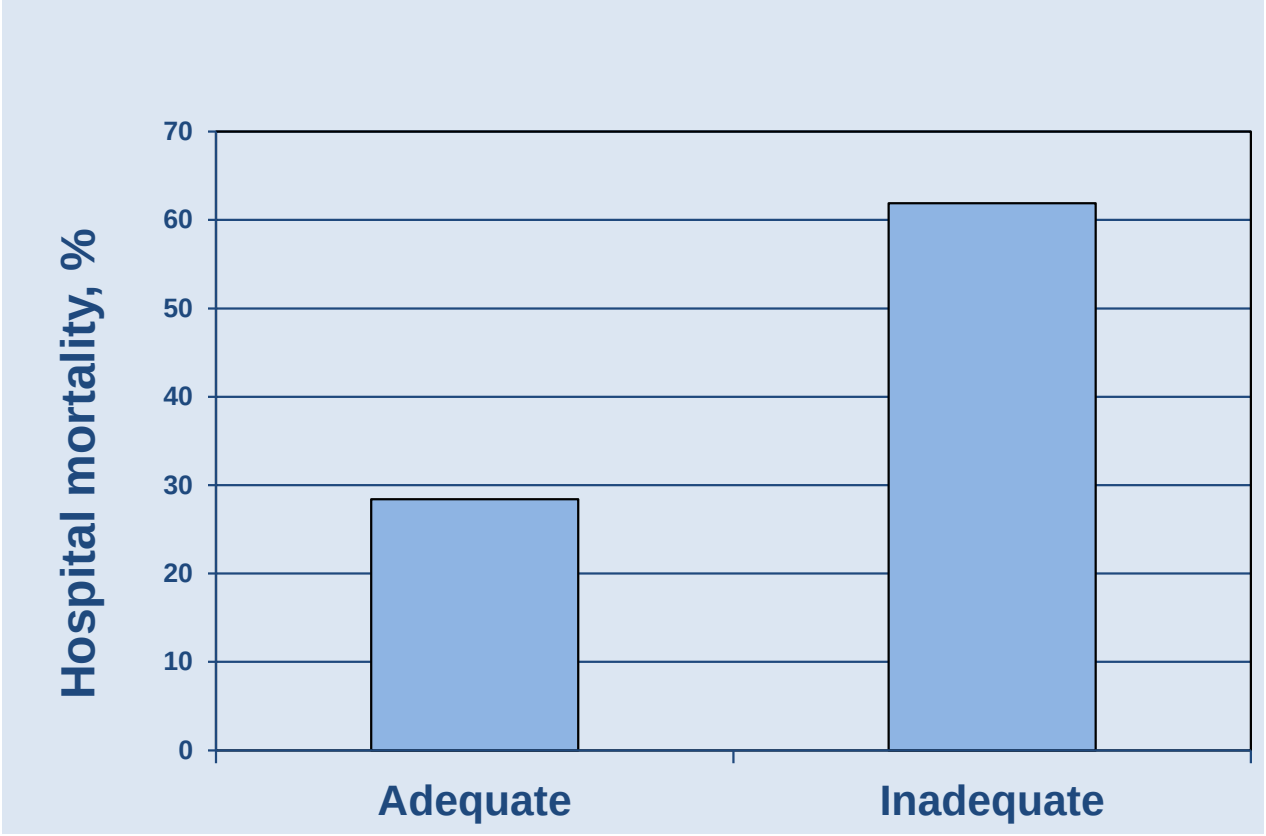
Impact of Delayed Appropriate Antimicrobial Therapy in Severe infections



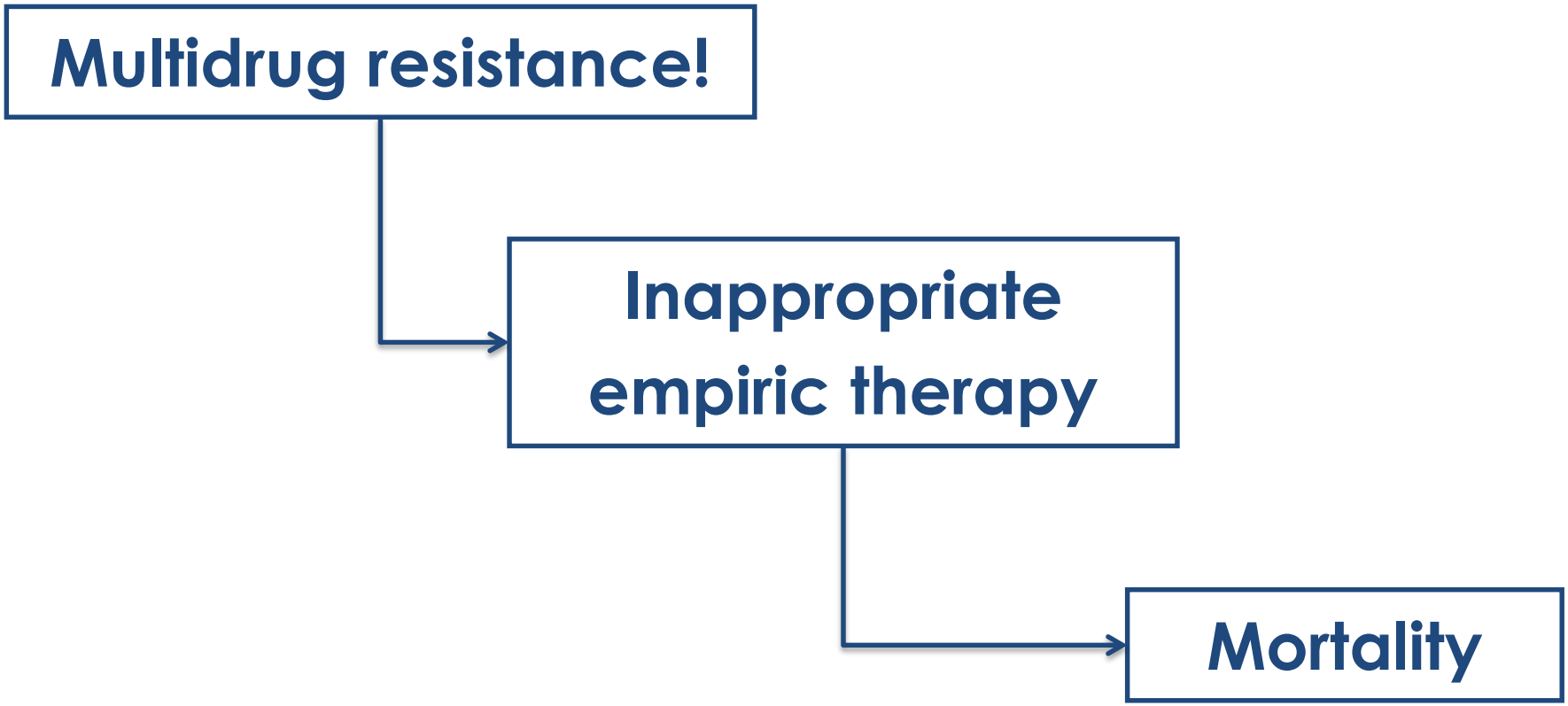
Critical time frame to start appropriate therapy: ≤24-48 hrs

Kollef et al. Chest 1999
Ibrahim et al. Chest: 2000

Empiric coverage of causative etiology

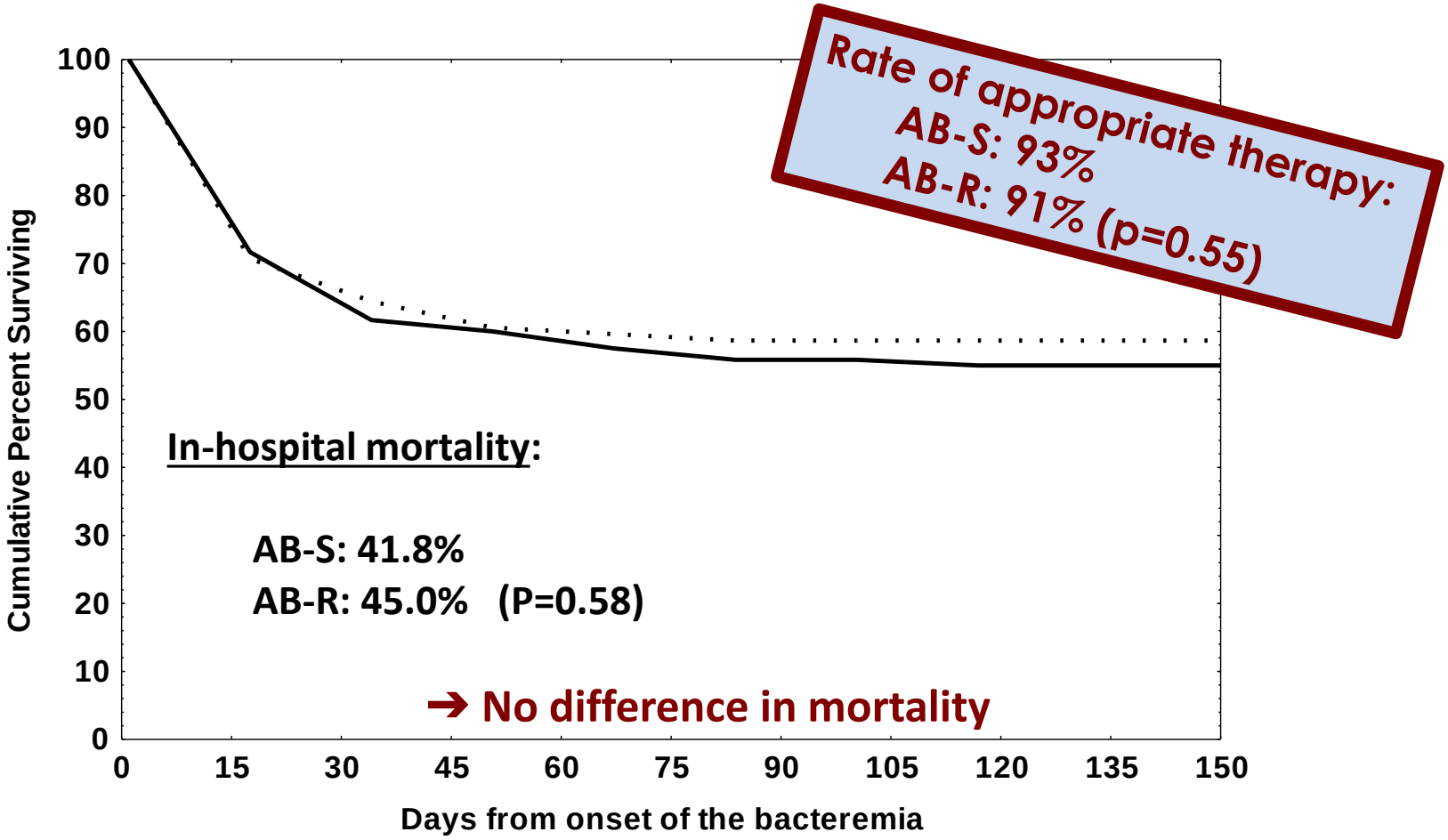
- At onset of sepsis the causative pathogens are unknown
- Culture results are generally available in 48 hrs
- Empiric ("blind") antimicrobial therapy must be started
- MD has to make an estimate of the most probable pathogens

Most important reason of empiric inappropriate antimicrobial therapy…



Relationship MDR & Mortality

Gram-negative bacteremia in ICU patients



Blot S, et al. Clin Infect Dis 2002

Strategies for appropriate empiric therapy

- **"Last-line" antibiotics up front**
  - Very broad empiric coverage
  - De-escalate to narrow spectrum once culture results are available
  - Concept proved to be save
  - Average % appropriate therapy 70-80%
  - Very often: not de-escalated
  - Triggers MDR development…

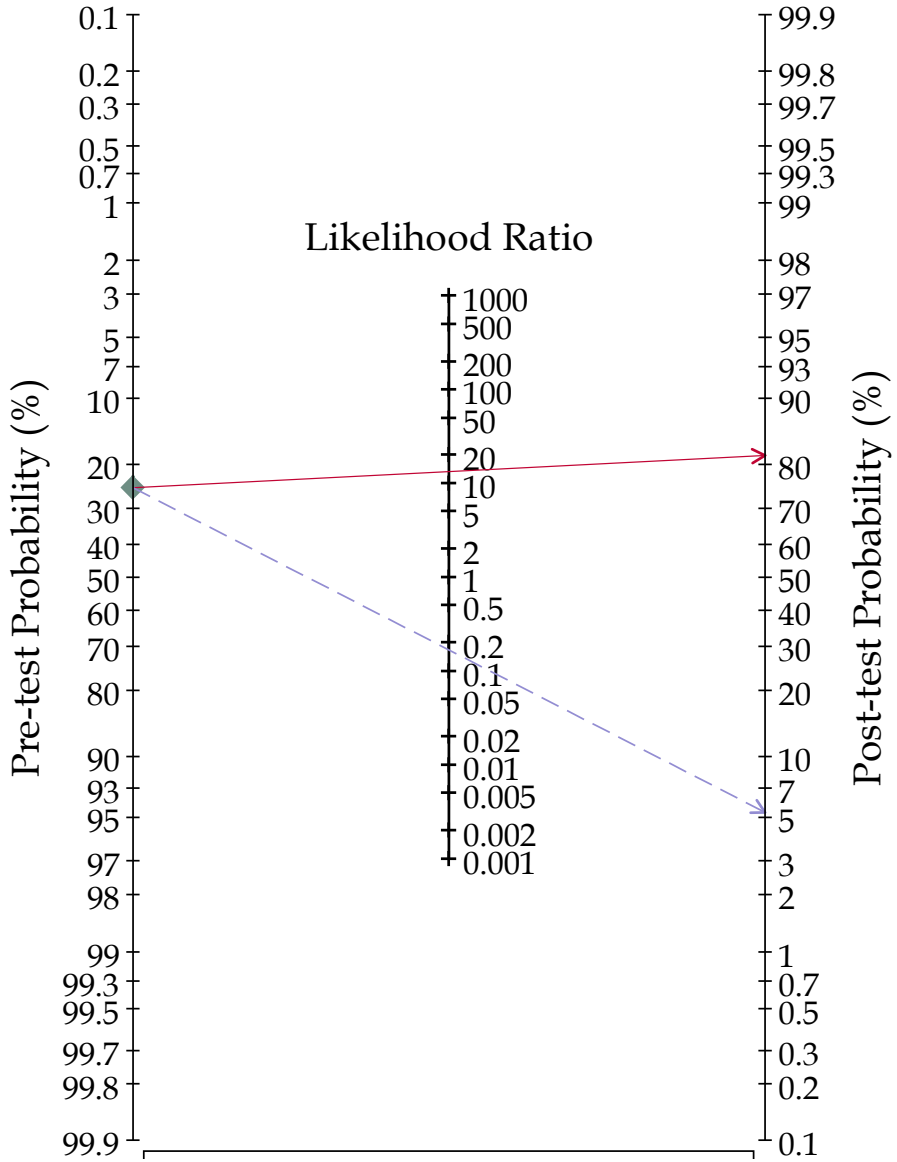
Strategies for appropriate empiric therapy

- **"Risk factor" –based**
  - Use "last-line" antibiotics in case of overt risk profile for MDR
  - Major risk factors for MDR:
    - Recent antibiotic exposure
    - Length of hospital stay >7 day
  - Rates of appropriate empiric therapy: 60-80%
  - Problem: classic risk factors for MDR have lost their predictive value

Strategies for appropriate empiric therapy

- **"Surveillance culture-assisted"**
  - Combines
    - risk profile for MDR
    - Colonization status of the patient
  - Results from routine surveillance cultures
    - Typical body sites screened in ICUs
      - Tracheal aspirates
      - Urine cultures
      - Rectal swab
      - Nasal swab
    - Initially used to detect and cohort/isolate MDR carriers

Can surveillance cultures predict MDR involvement in HAI (bacteremia/pneumonia)?

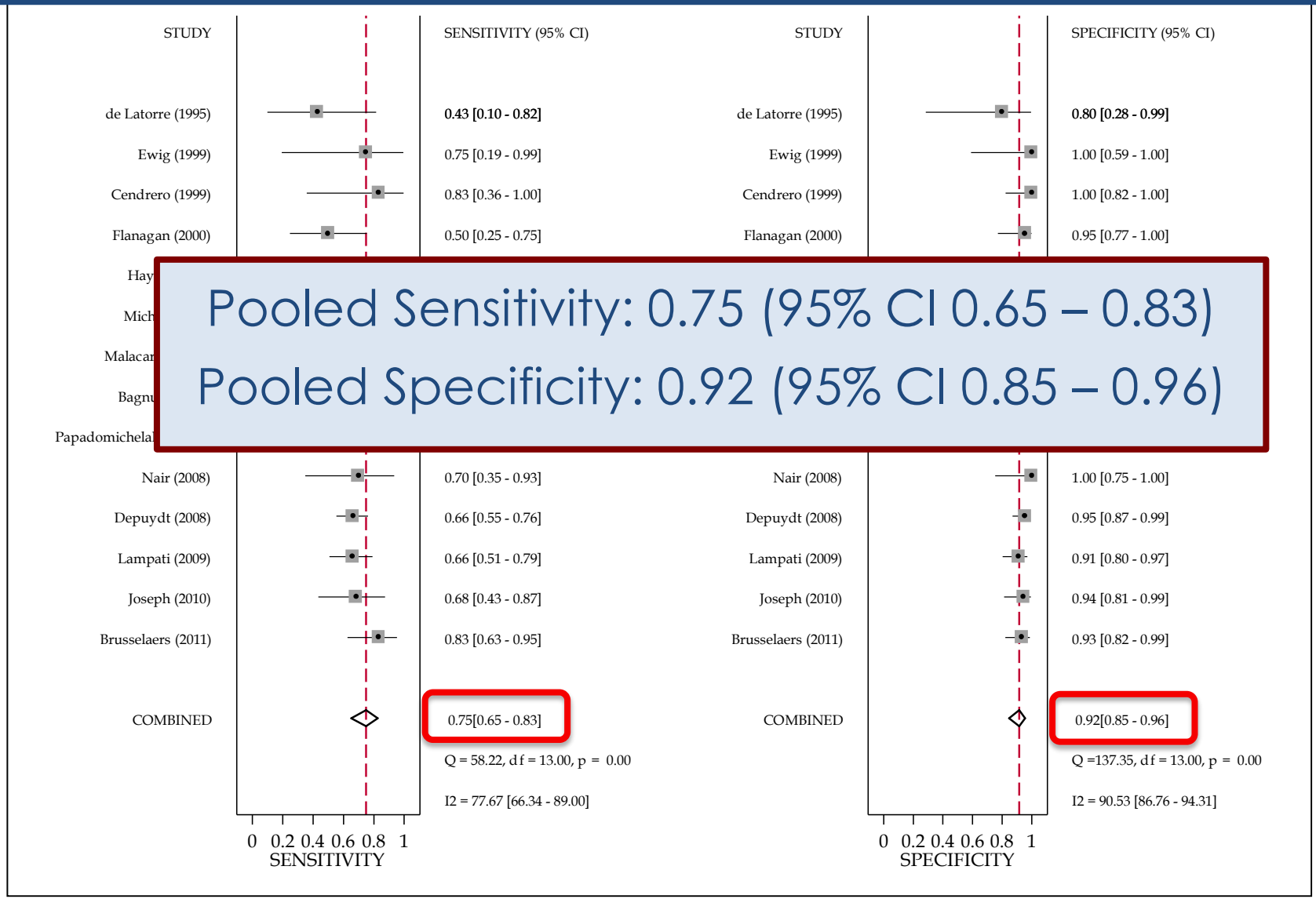


Fagan plot:

Pre- and post-test likelihood for VAP to be caused by MDR pathogens

Brusselaers N, et al. Intensive Care Med 2012

Sensitivity & specificity of surveillance cultures to predict MDR in ventilator-associated pneumonia



Pooled Sensitivity: 0.75 (95% CI 0.65 – 0.83)

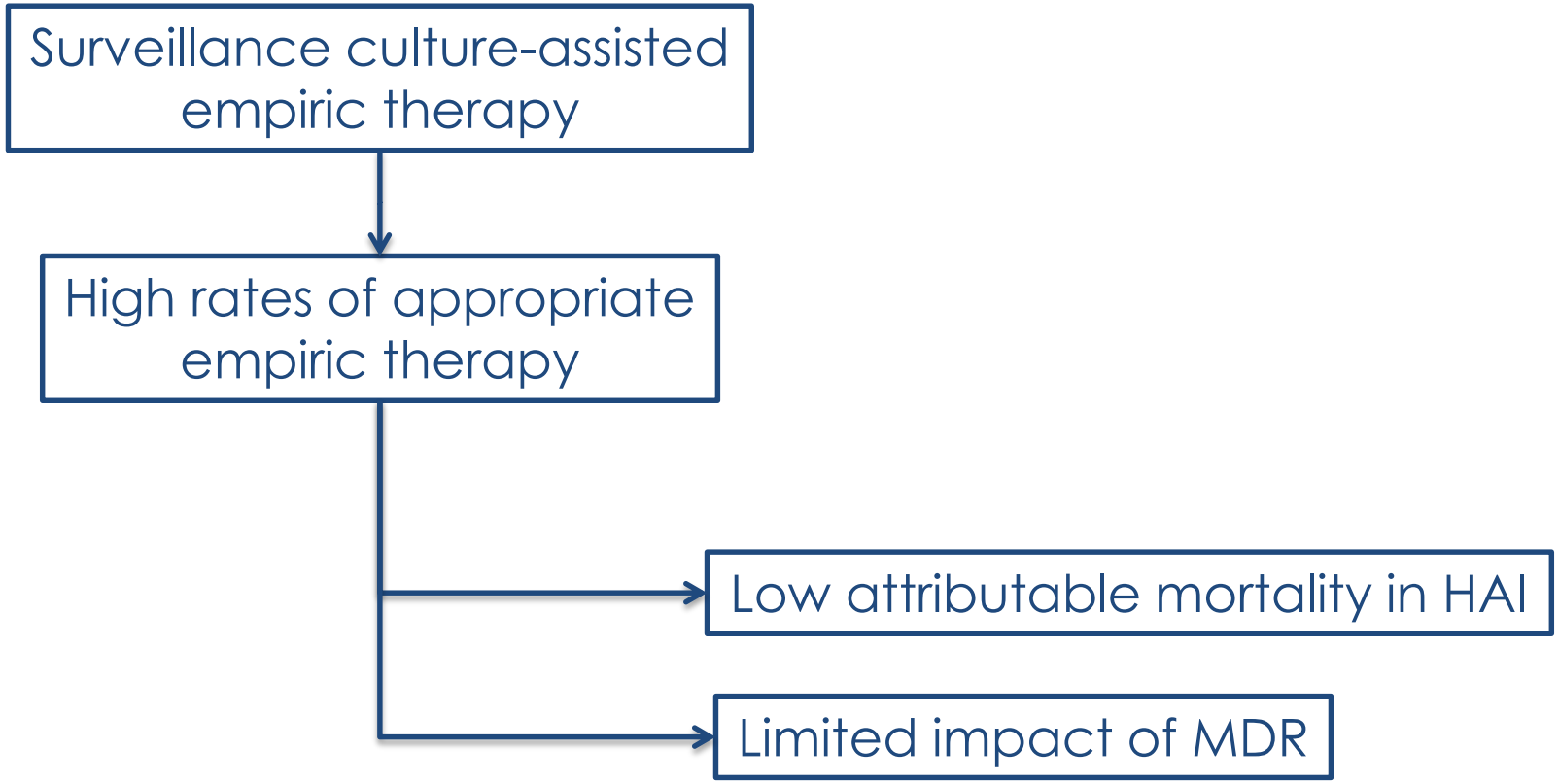
Pooled Specificity: 0.92 (95% CI 0.85 – 0.96)

Brusselaers N, et al. Intensive Care Med 2012

"Surveillance culture"–assisted empiric therapy increases the likelihood of appropriatenes

Author ,y (infection)	Comparator guideline	Appropriate empiric therapy		P
		Strict empiric scheme	Surveillance culture assisted	
Jung B, 2008 (VAP)	ATS 2005	71%	85%	0.04
Depuydt P, 2006 (Bacteremic pneumonia)	IDAB 2002	75%	90%	<0.05
Michel F, 2002 (VAP)	ATS 1996 Trouillet 1998	68% 83%	95%	0.005 0.15
Depuydt P, 2008 (MDR VAP)	Carbapenem (ATS 2005) B-lact.+QUI (Trouillet 1998) B-lact.+aminoside (Trouillet '98)	81% 56% 68%	77%	>0.05 <0.05 0.06

Assumption



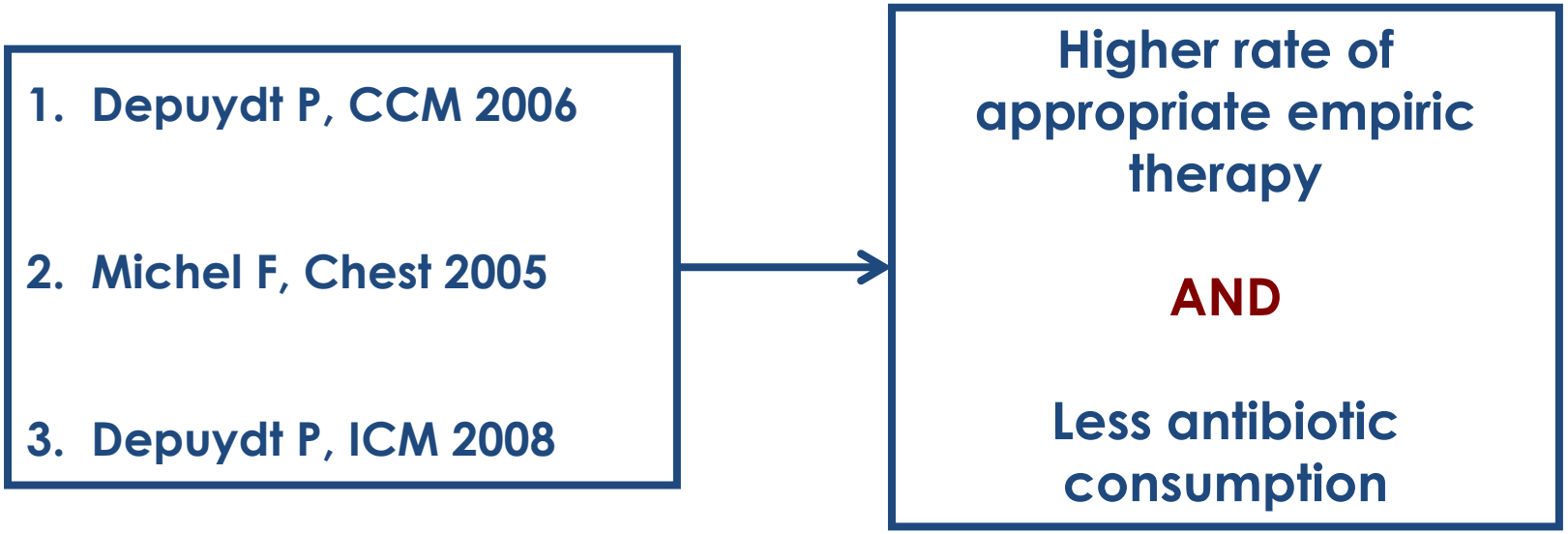
Blot S. Clin Microbiol Infect 2008

High NPV… "Surveillance culture"–assisted empiric therapy decreases antibiotic consumption

Antibiotic class	% of observed prescriptions (SC assisted)	Hypothetical prescription	
		ATS (1996)	Trouillet (1998)
Carbapenems, Antipseudomonal cephalosporins, Antipseudomonal penicillins	45%	80% (p=0.002)	76% (p=0.01)

Michel F, Chest 2005

High NPV… "Surveillance culture"–assisted empiric therapy decreases antibiotic consumption



Essentials in Anti-Infective Management

1. Early recognition of sepsis
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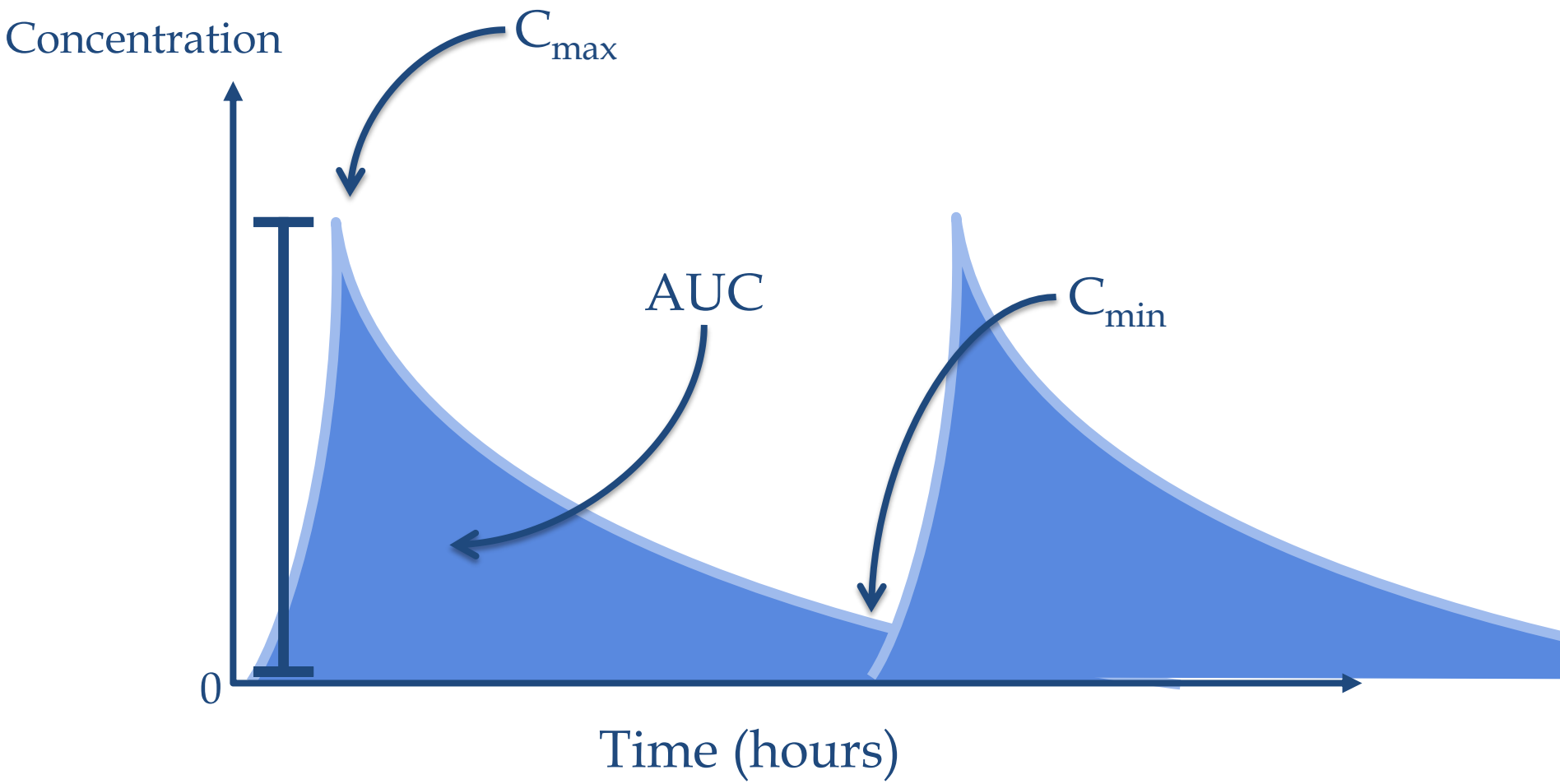
Basic conditions for optimal antibiotic therapy

Adequate dosing

- Maximize of "*Bacterial killing capacity*"
- Minimize risk of resistance development (caused by underdosing)
- Minimize adverse effects (caused by overdosing)

Pharmacokinetics (PK)



Pharmacokinetics (PK)

- PK only describes concentration-time curve

- PK does not provide information on antibiotic activity (i.e. “bacterial killing”)

Pharmacodynamics (PD)

PD ➔ relation between AB concentration and effect on pathogen

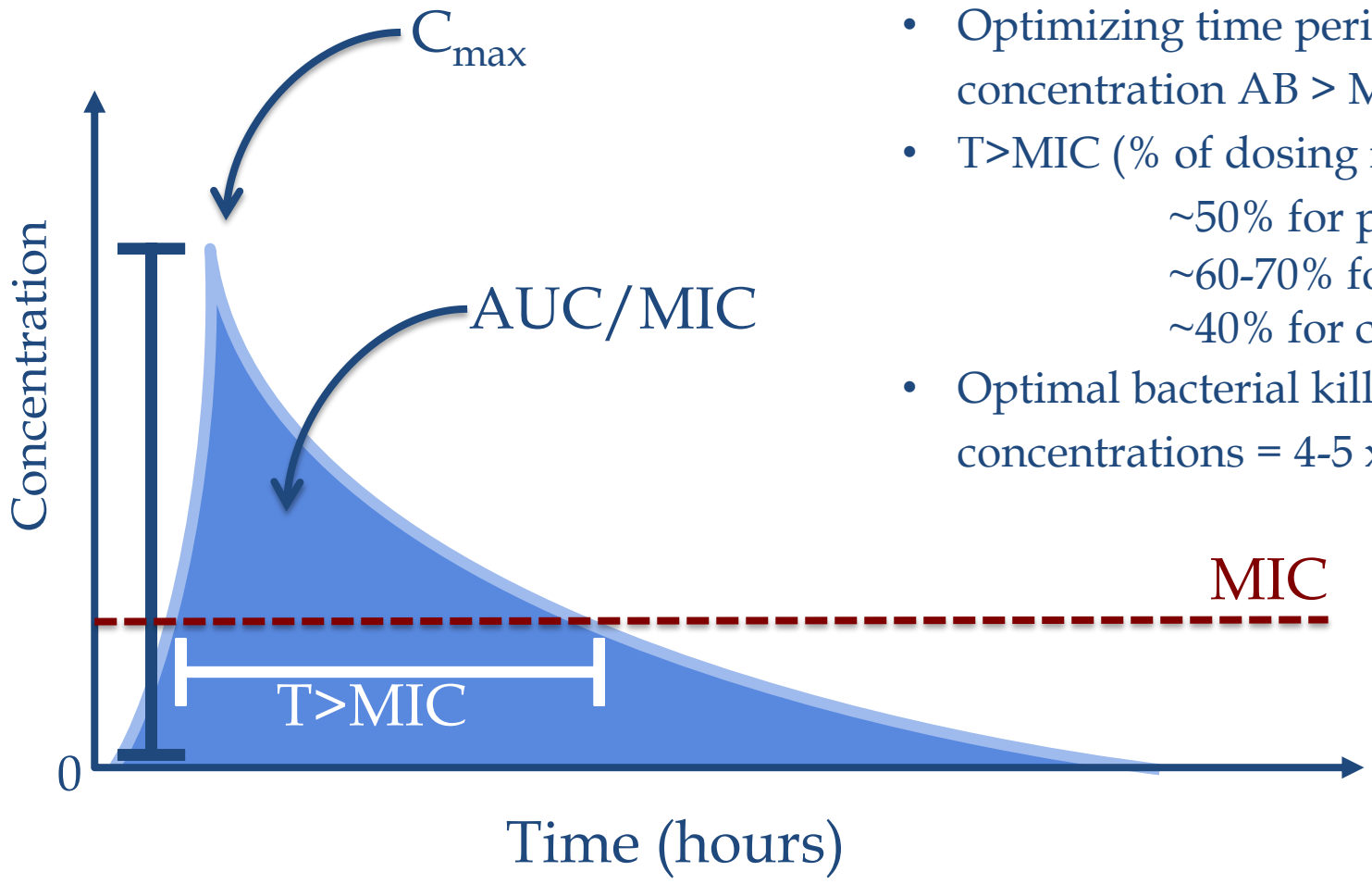
- **(!) MIC**, minimal inhibitory concentration

- Three classes of antibiotics:

  - Time-dependent
  - Concentration-dependent
  - Concentration-dependent with time-effect

Pharmacodynamics (PD)

- Time-dependent antibiotics

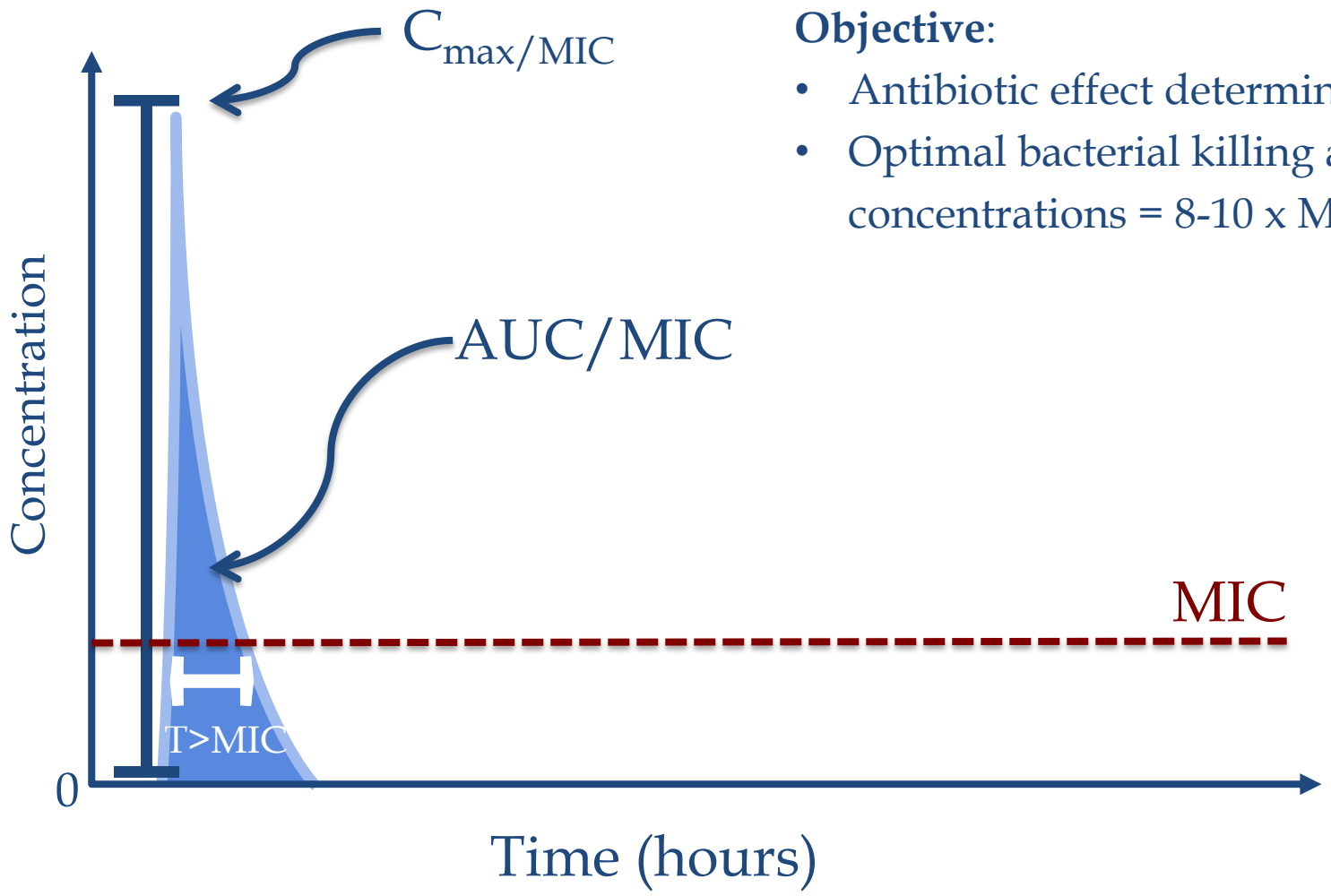


Objective:

- Optimizing time period in which concentration AB > MIC
- T>MIC (% of dosing interval):
  - ~50% for penicillins
  - ~60-70% for cephalo's
  - ~40% for carbapenems
- Optimal bacterial killing at AB concentrations = 4-5 x MIC

Pharmacodynamics (PD)

- Concentration-dependent antibiotics



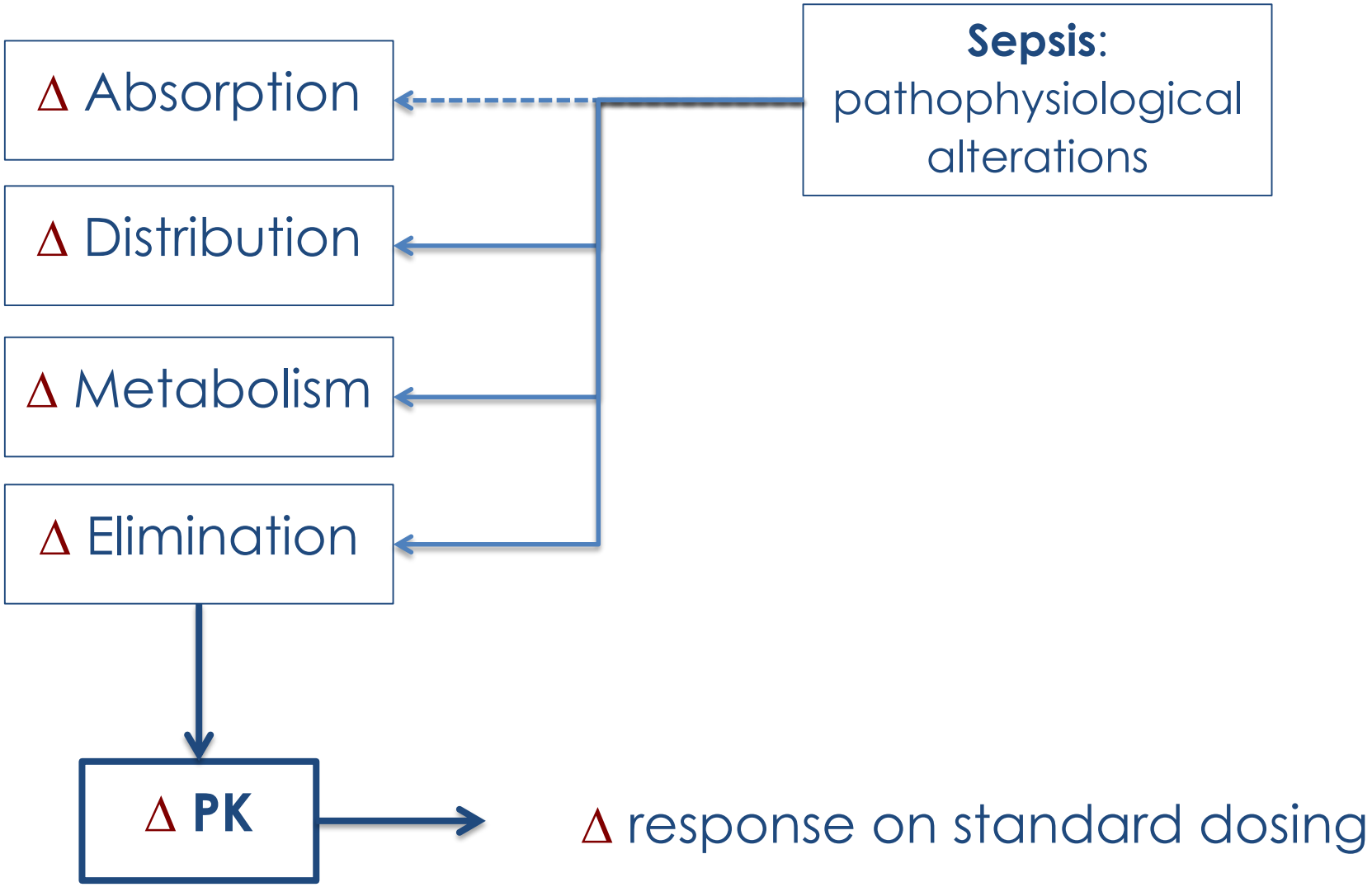
Objective:

- Antibiotic effect determined by C_{max}
- Optimal bacterial killing at AB concentrations = 8-10 x MIC

Mechanisms leading to PK of an antibiotic agent

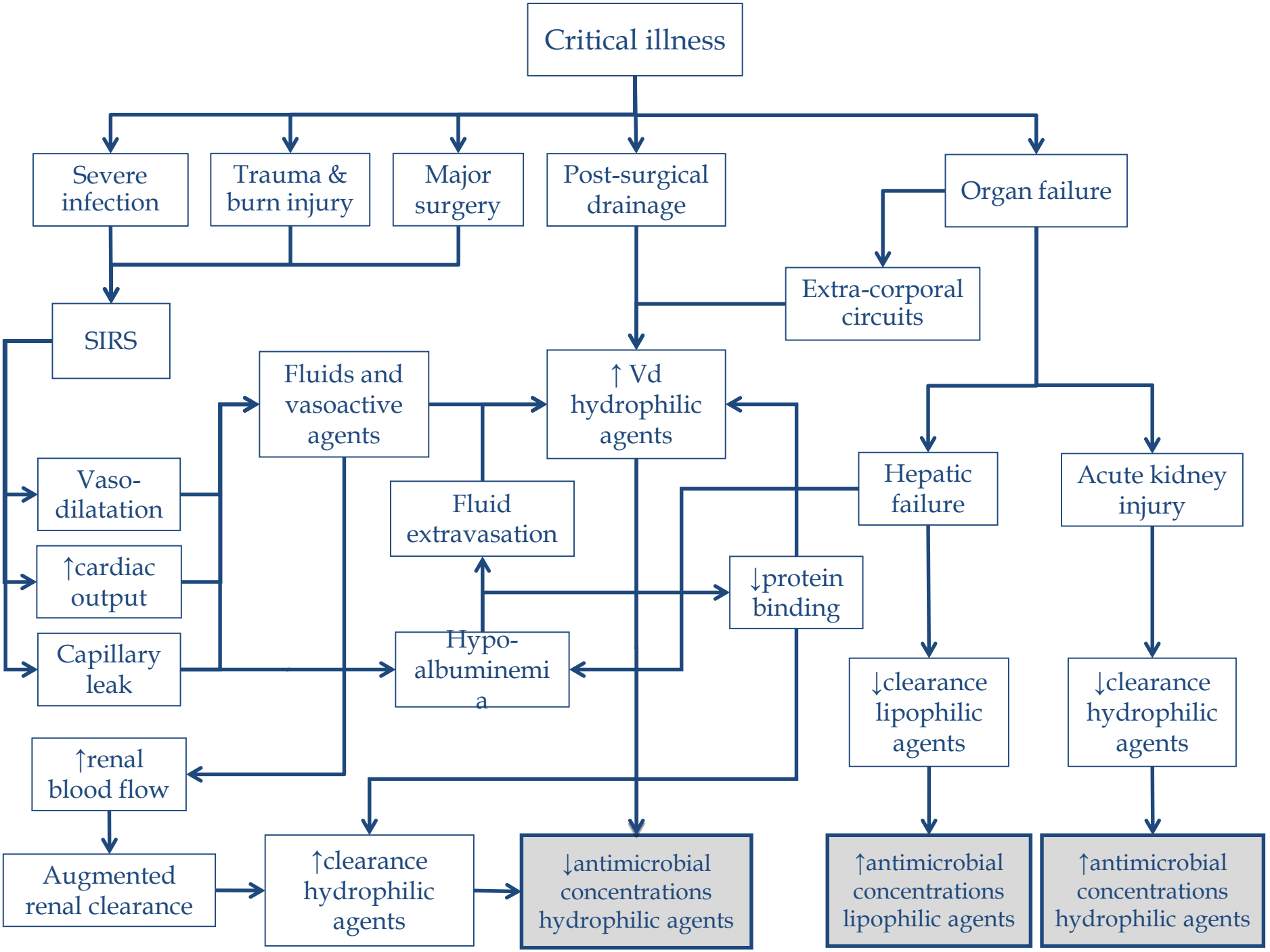
- Non-critically ill patients
  - Stable processes
  - PK = predictable
  - Standard doses ➔ desired [AB]

Mechanisms leading to PK of an antibiotic agent



The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents ☆

Blot S, Pea F, Lipman J. Adv Drug Deliv Rev 2014

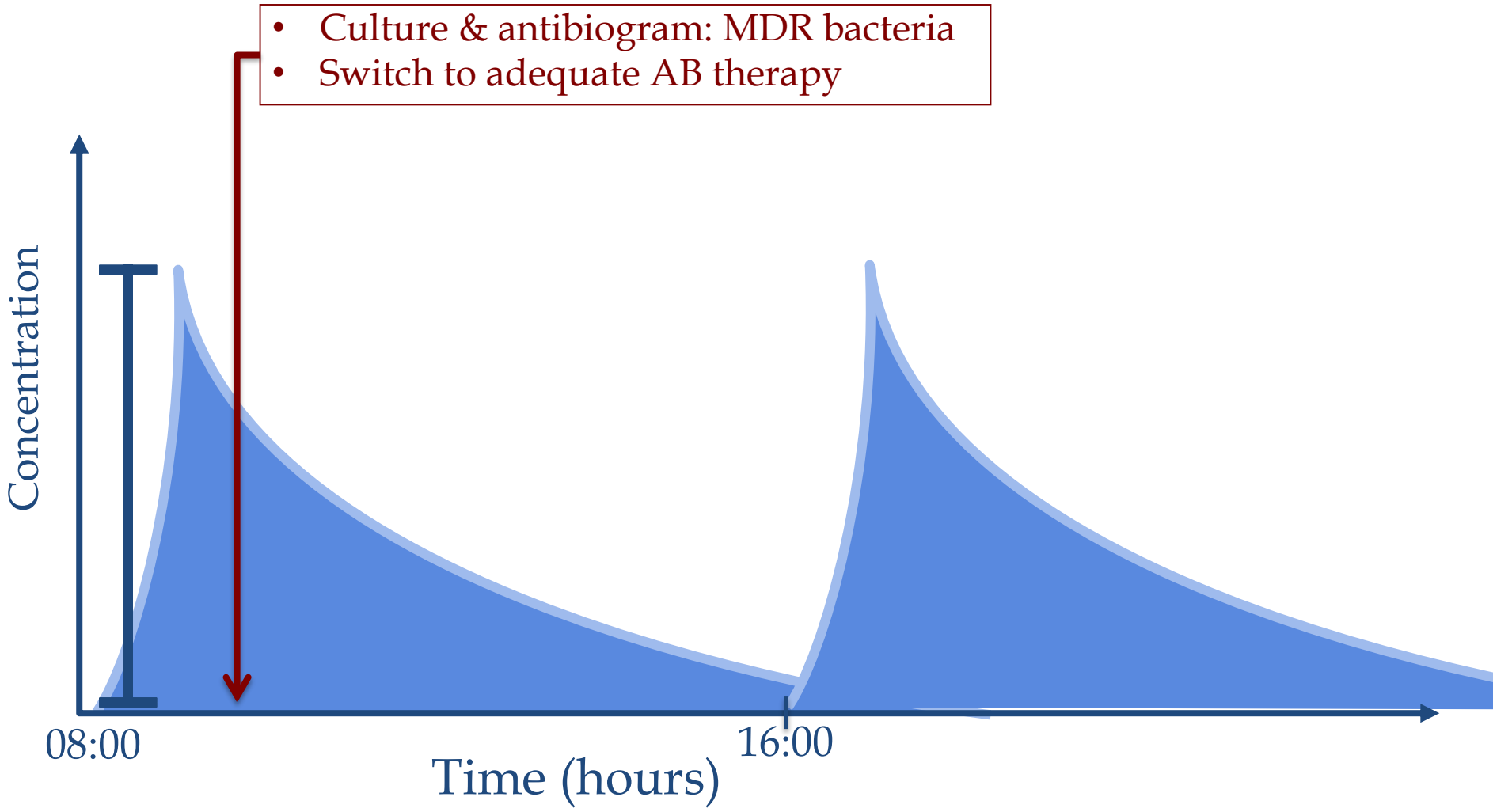

Critical illness
Severe infection
Trauma & burn injury
Major surgery
Post-surgical drainage
Organ failure
Extra-corporal circuits
SIRS
Fluids and vasoactive agents
↑ Vd hydrophilic agents
Vaso-dilatation
↑cardiac output
Capillary leak
Fluid extravasation
↓protein binding
Hypo-albuminemia
Hepatic failure
Acute kidney injury
↓clearance lipophilic agents
↓clearance hydrophilic agents
↑renal blood flow
Augmented renal clearance
↑clearance hydrophilic agents
↓antimicrobial concentrations hydrophilic agents
↑antimicrobial concentrations lipophilic agents
↑antimicrobial concentrations hydrophilic agents

PK of antibiotics in severe sepsis…

- Overdosing and toxicity is possible in context of organ failure
- Plenty of other factors (sometimes in the same patient) might cause underdosing through ↑Vd and ↑clearance.
- Risk of underdosing (with hydrophilic antibiotics) is a greater threat than risk of overdosing
- Errors in the administration of ABs (might)↑risk of underdosing

Nursing point of interest

(!) Do not postpone start new AB in case of switch



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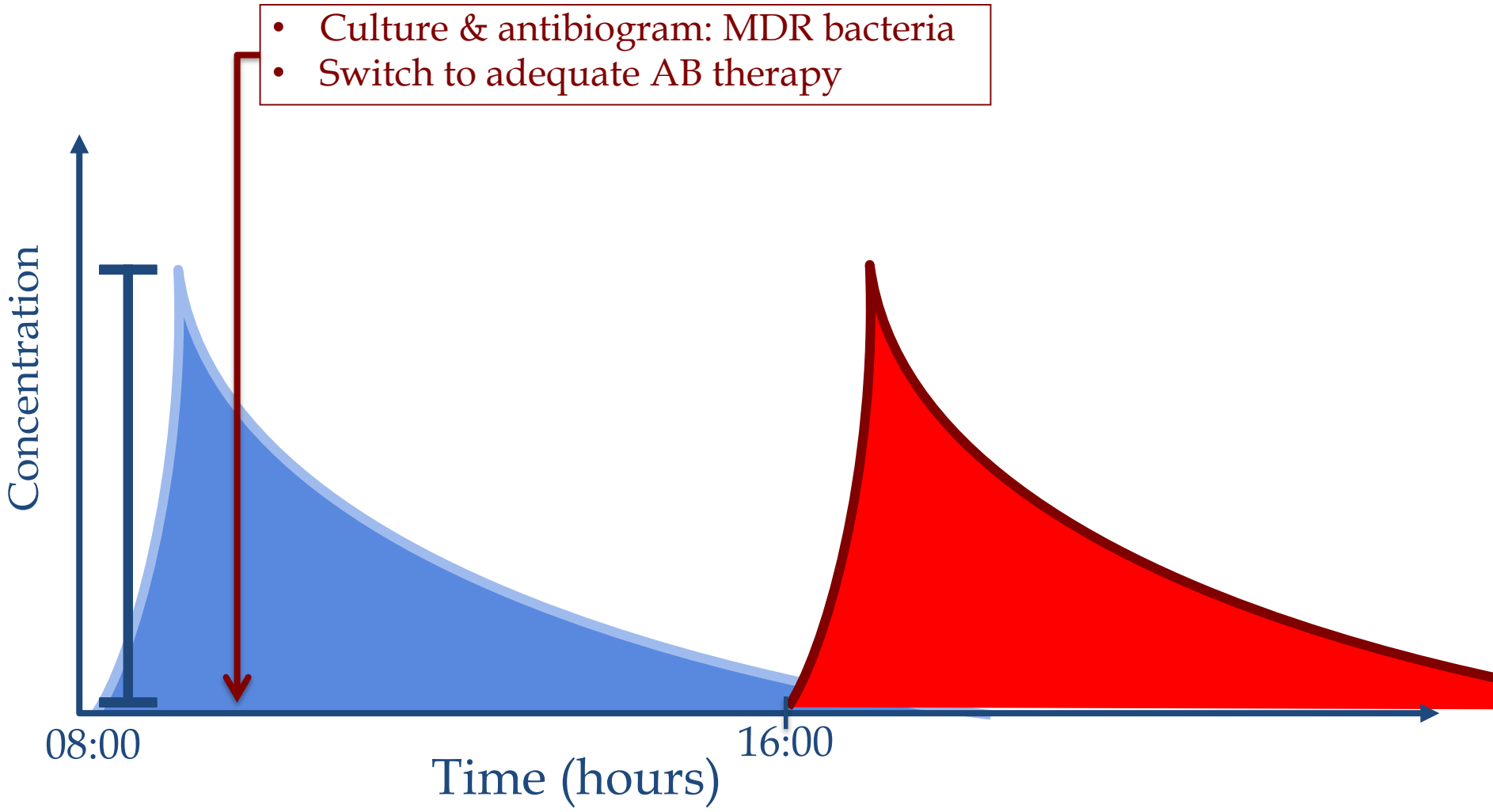

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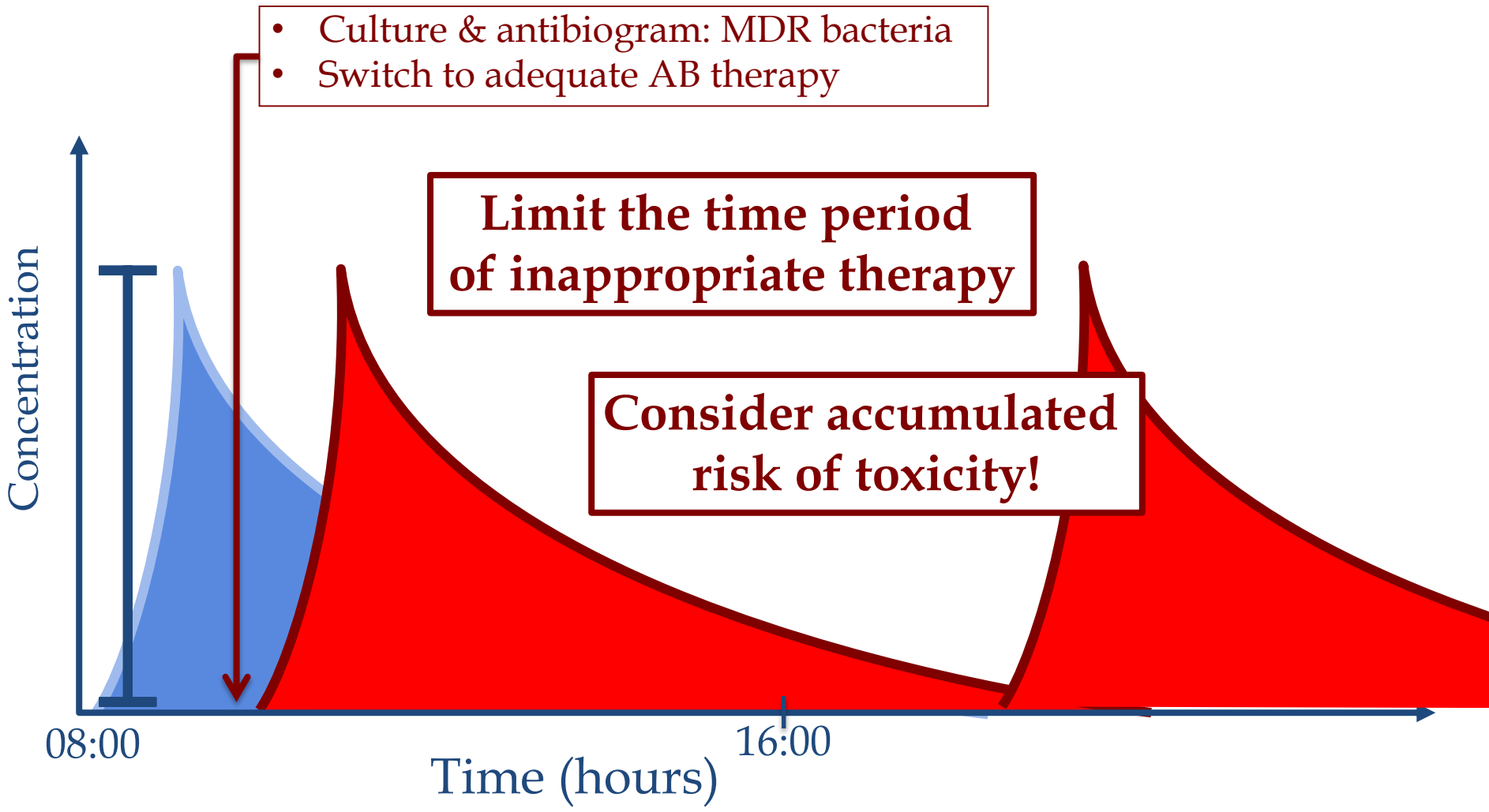
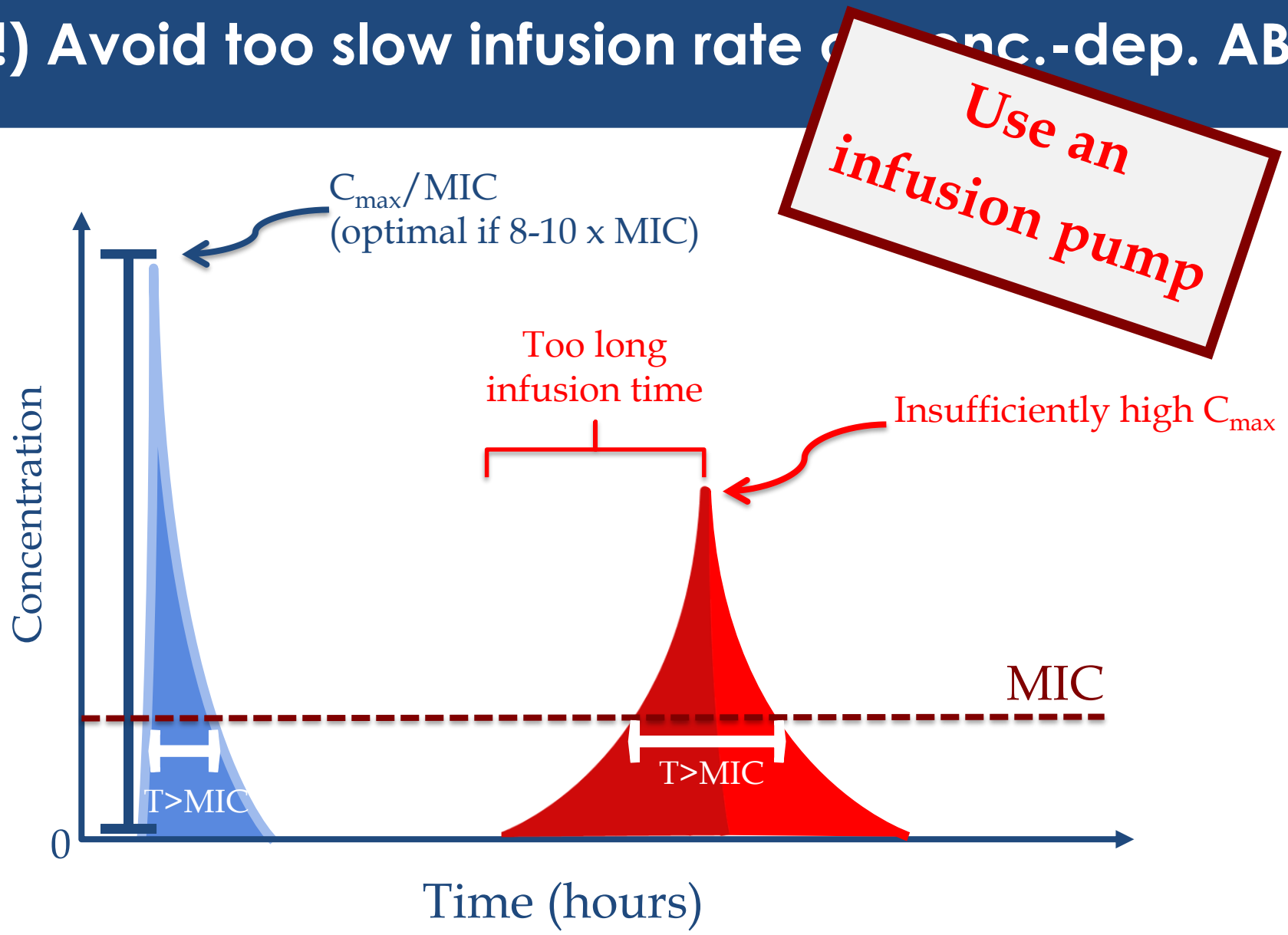


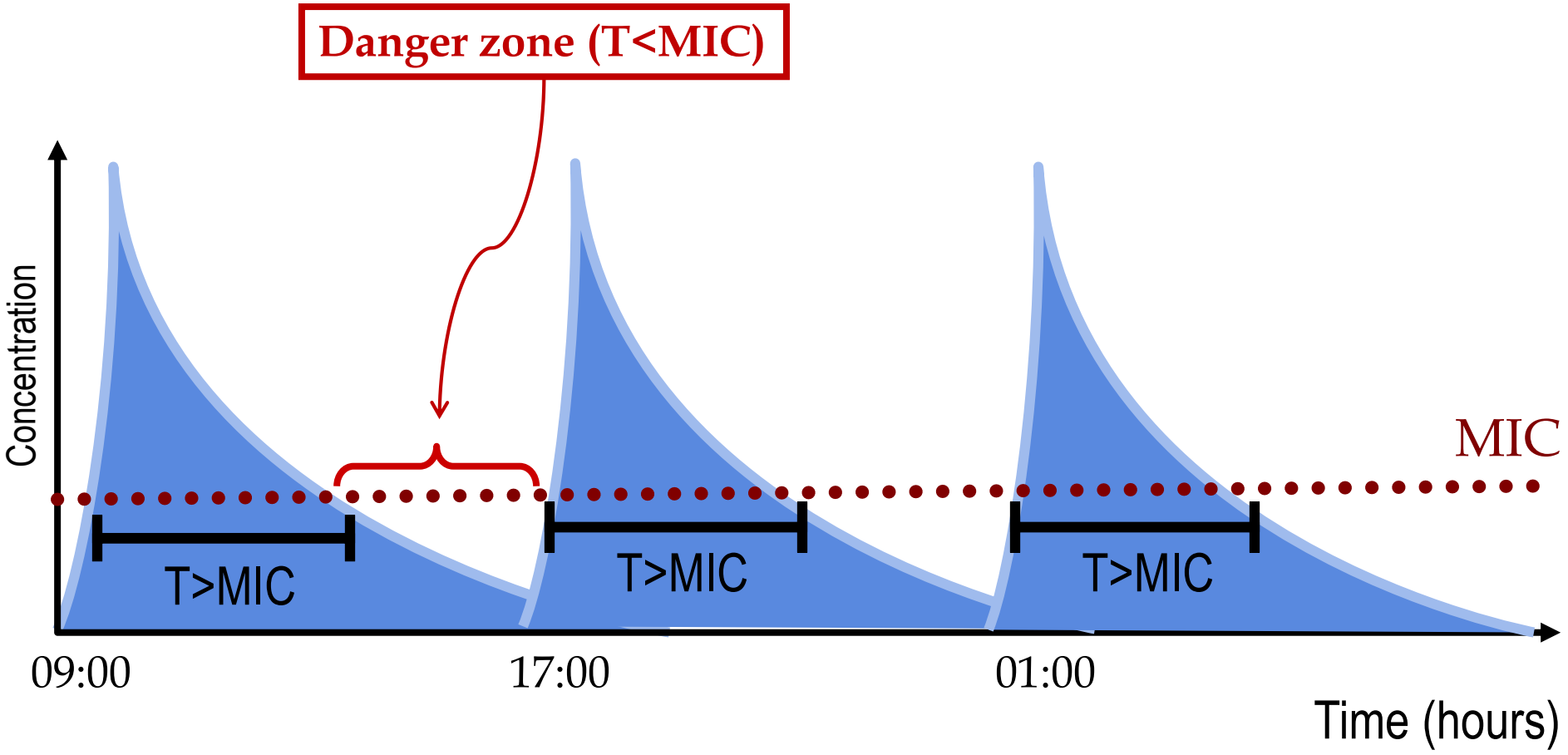
Nursing point of interest

(!) Avoid too slow infusion rate of conc.-dep. AB



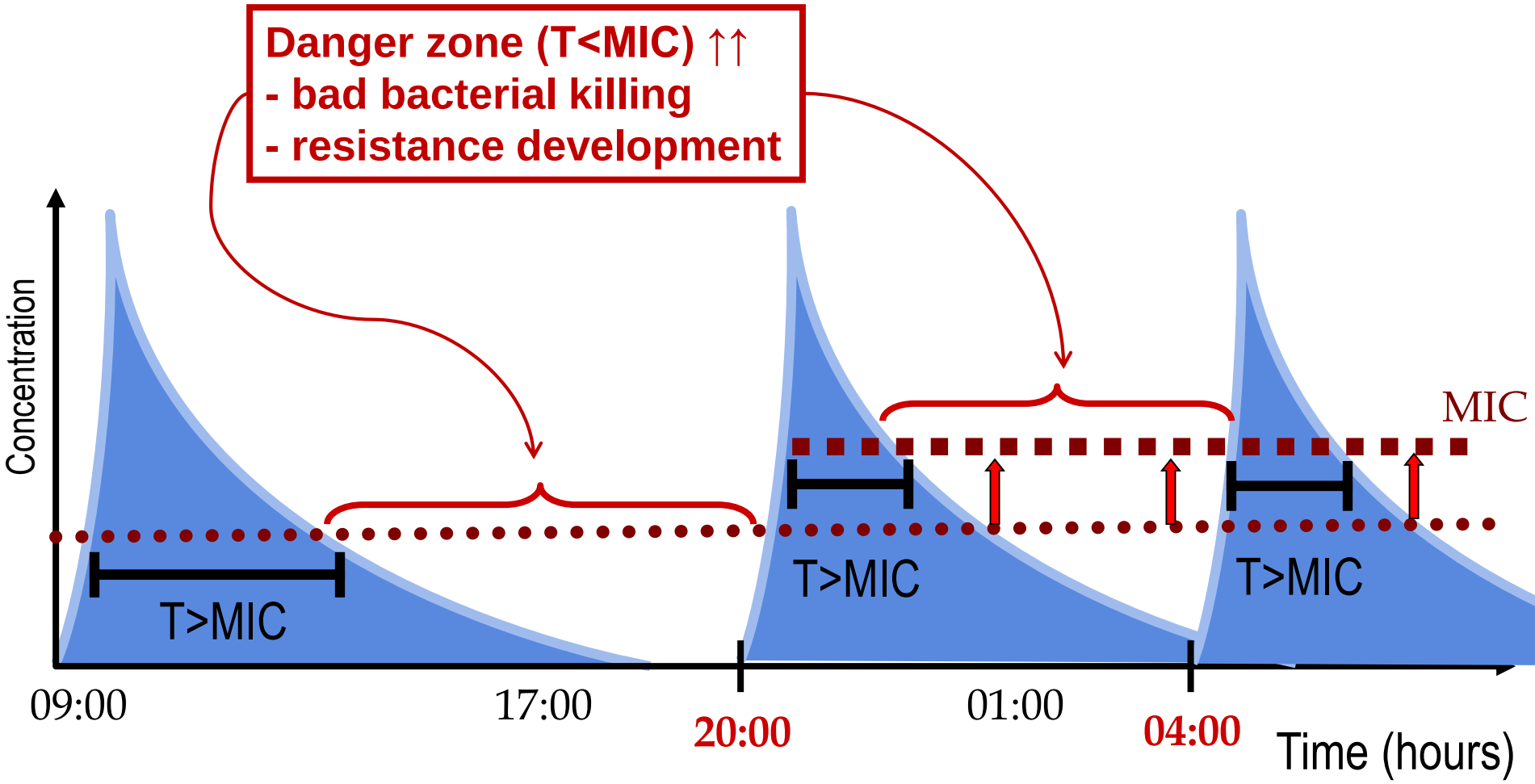
Nursing point of interest

(!) Do not increase time interval of time-dep. AB



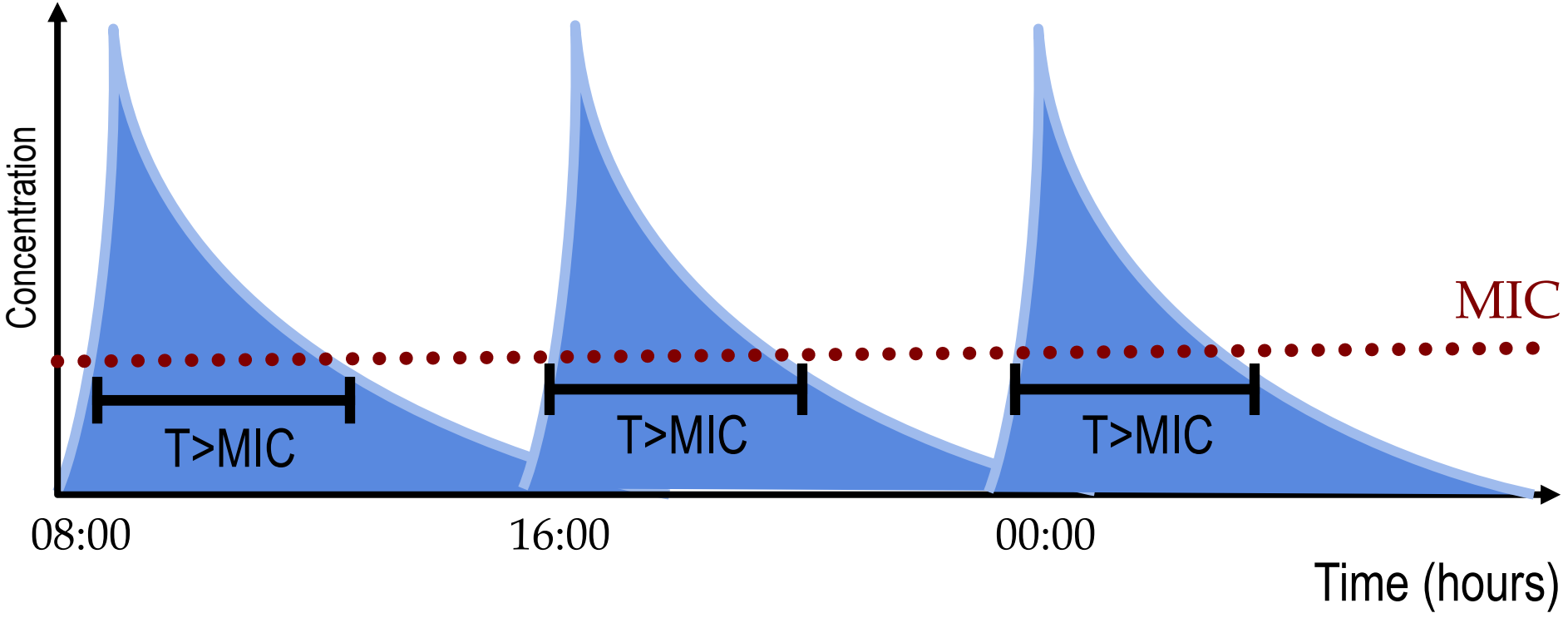
Nursing point of interest

(!) Do not increase time interval of time-dep. AB



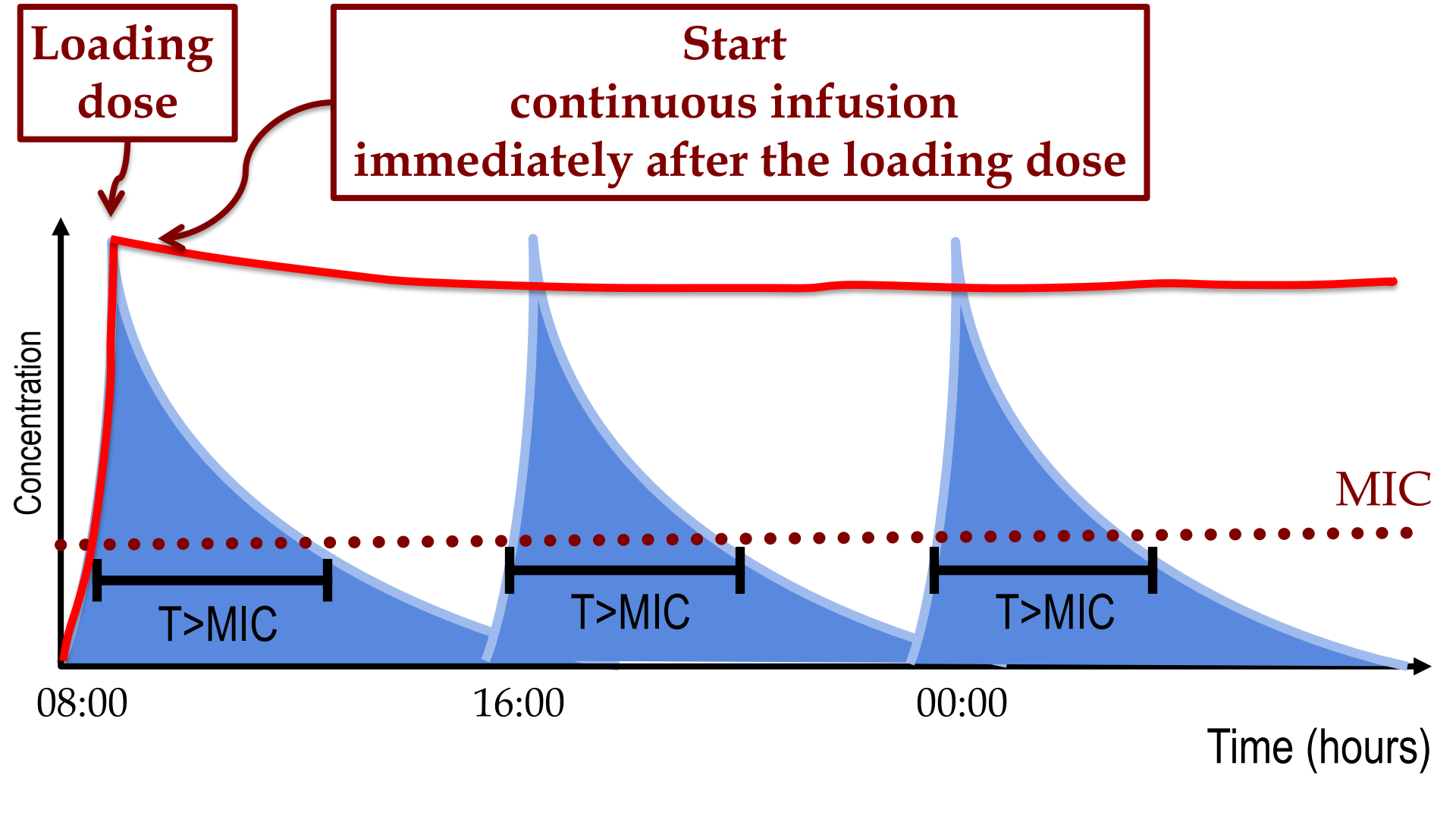
Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.



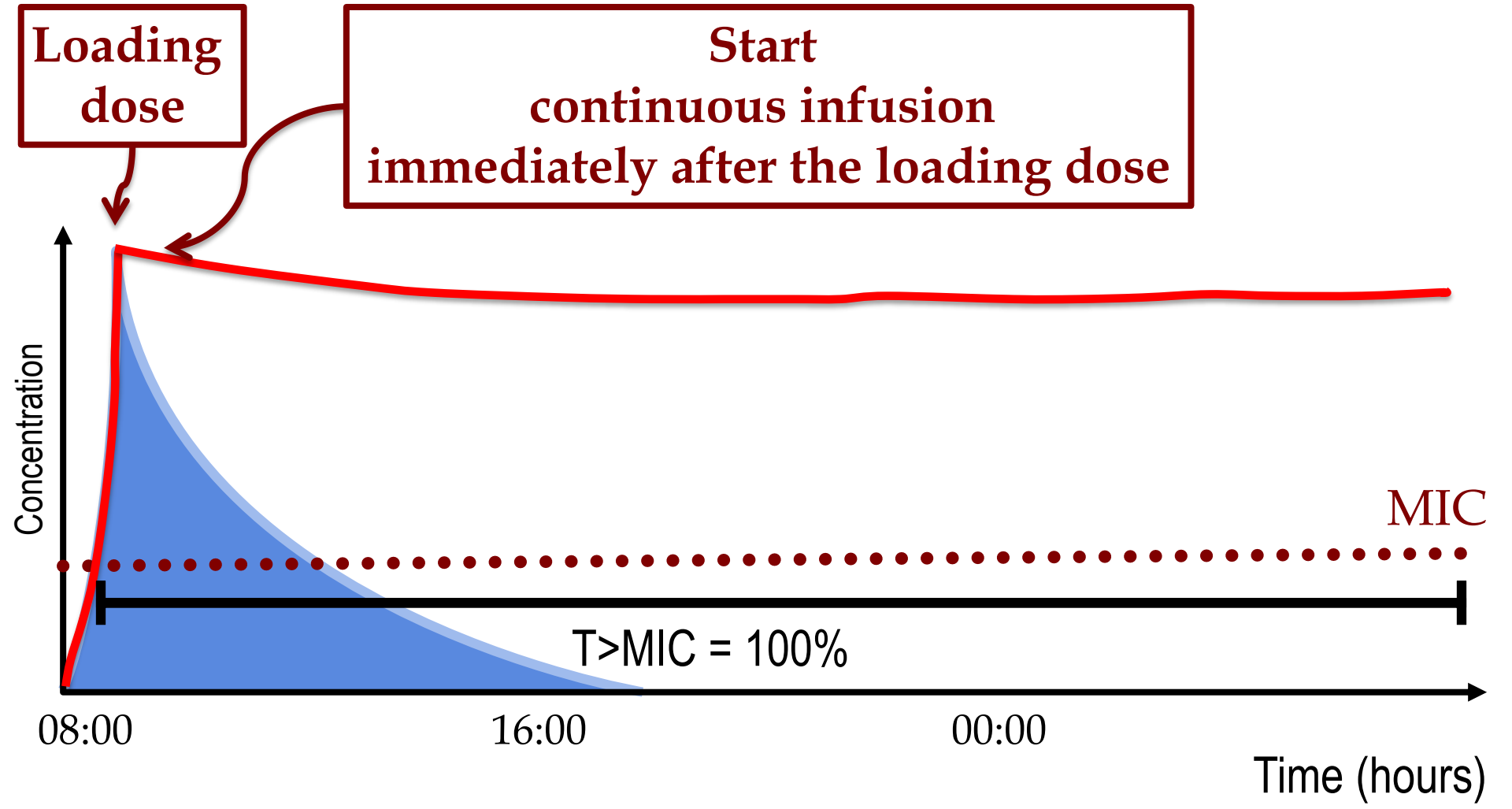
Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.



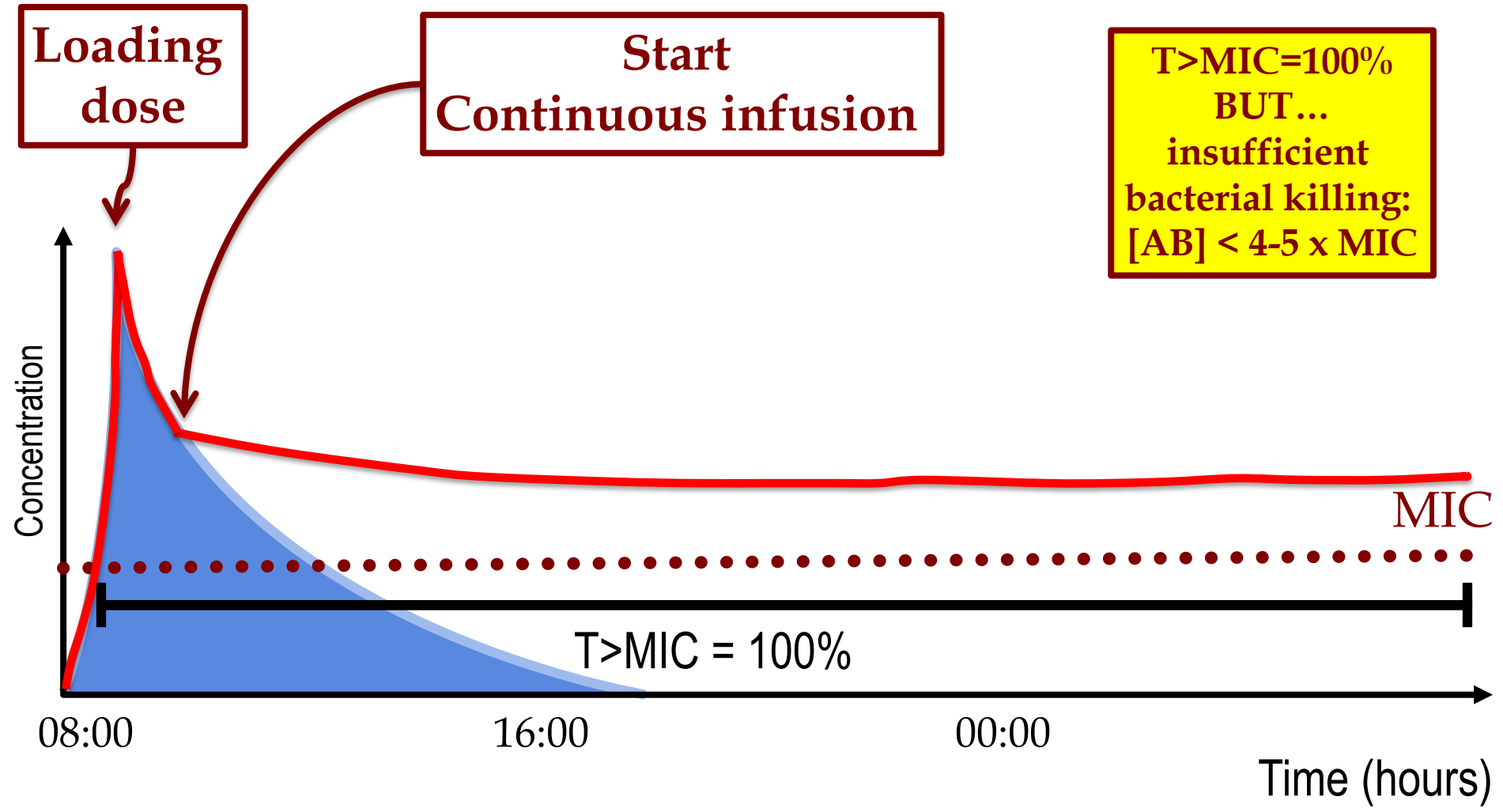
Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.



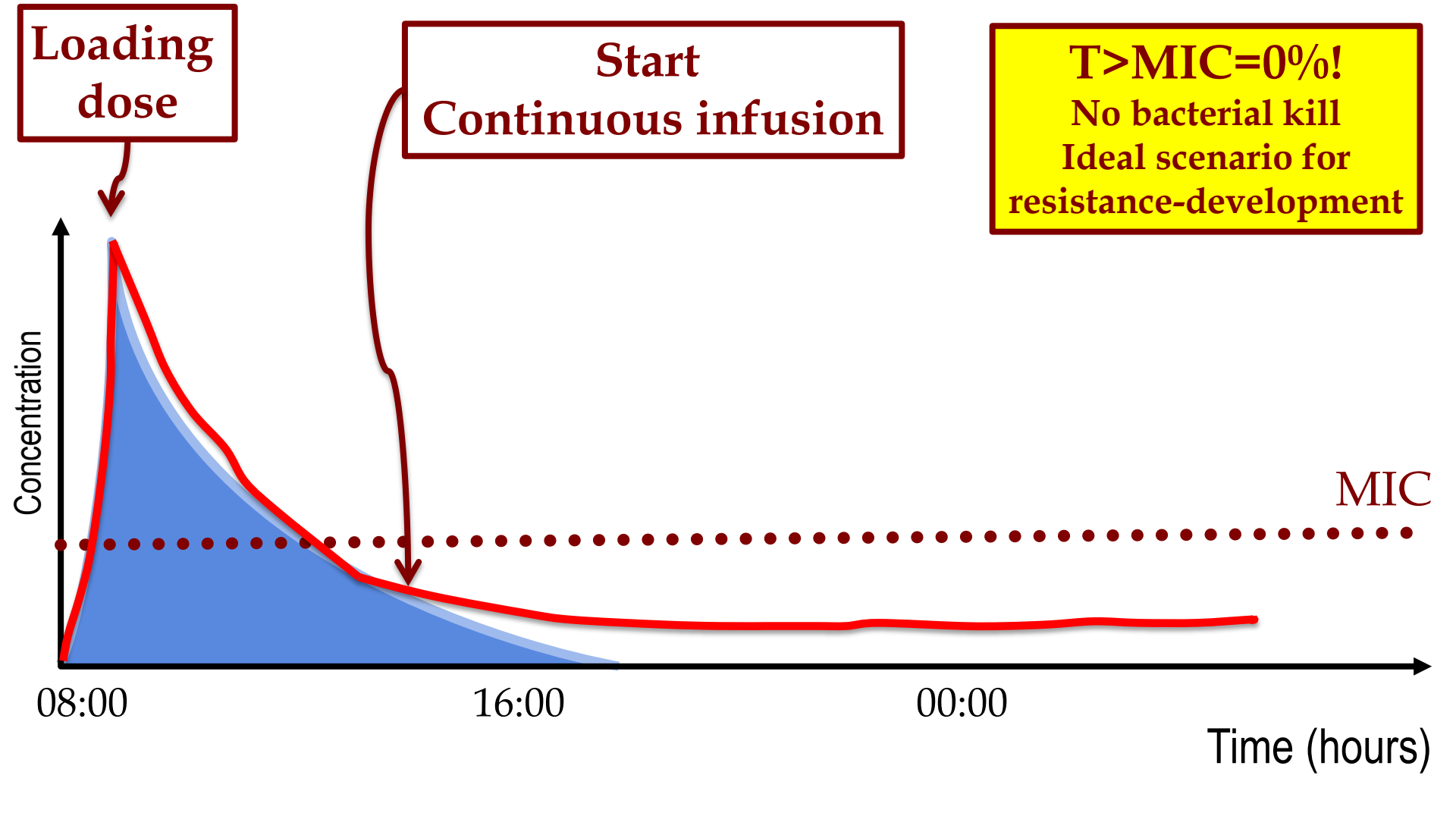
Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.



Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.



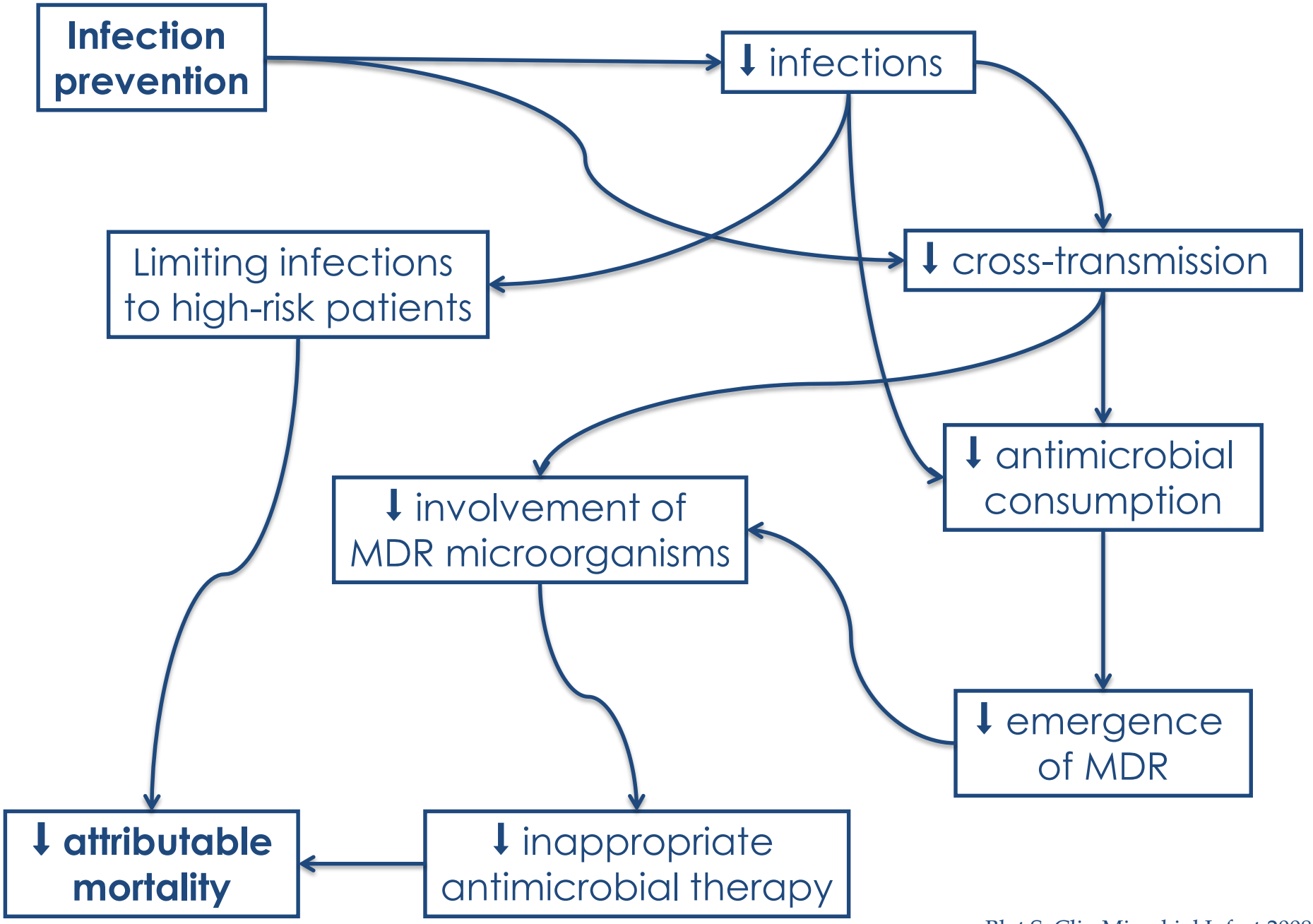
Nursing point of interest - **Continuous infusion**

(!) No time between loading dose and C.I.

- Failure to initiate continuous infusion immediately after the loading dose…
  - Inform physician
  - Await a second intermittent dose to start C.I.
  - Idea: start C.I. together with loading dose

Essentials in Anti-Infective Management

1. Early recognition of sepsis
2. First shot antimicrobial therapy: asap
3. Coverage of causative etiology
4. Adequate dosing
5. Infection prevention



Blot S. Clin Microbiol Infect 2008

Conclusion

1. HAI are associated with high morbidity and mortality
2. Attributable mortality can be limited
    - Early recognition of sepsis
    - 3 basic conditions for optimal antibiotic therapy
3. HAI prevention remains pivotal